(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau

(43) International Publication Date
10 January 2008 (10.01.2008)

PCT

(10) International Publication Number
WO 2008/005519 A3

(51) International Patent Classification:
C07D 403/14 (2006.01) *A61P 31/12* (2006.01)
A61K 31/4353 (2006.01)

(21) International Application Number:
PCT/US2007/015553

(22) International Filing Date: 6 July 2007 (06.07.2007)

(25) Filing Language: English

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(30) Priority Data:

60/819,289	7 July 2006 (07.07.2006)	US
60/832,403	21 July 2006 (21.07.2006)	US
60/832,769	24 July 2006 (24.07.2006)	US

(71) Applicants *(for all designated States except US)*: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US). **K.U. LEUVEN RESEARCH & DEVELOPMENT** [BE/BE]; Minderbroedersstraat 8A, B-3000 Leuven (BE). **PUERSTINGER, Gerhard** [AT/AT]; Badhausstrasse 10/4, A-6080 Igis (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BONDY, Steven, S.** [US/US]; 95 Hillview Drive, Danville, CA 94506 (US). **DAHL, Terrence, C.** [US/US]; 1646 Kennewick Drive, Sunnyvale, CA 94087 (US). **OARE, David, A.** [US/US]; 1622 Ralston Avenue, Belmont, CA 94002 (US). **OLIYAI, Reza** [US/US]; 3284 La Mesa Drive #2, San Carlos, CA 94070 (US). **TSE, Winston, C.** [US/US]; 1128 Shoreline Drive, San Mateo, CA 94404 (US). **ZIA, Vahid** [US/US]; 53 Maple Way, San Carlos, CA 94070 (US).

(74) Agents: **KUTZENCO, Allan, N.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

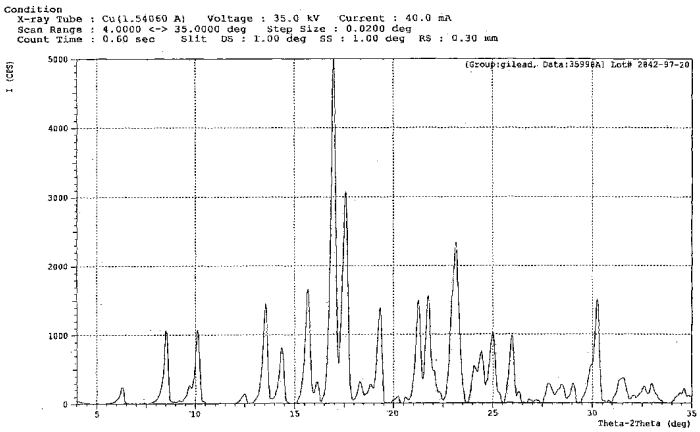
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

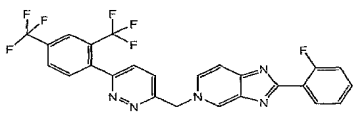
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) **Title:** NOVEL PYRIDAZINE COMPOUND AND USE THEREOF





(1)

(57) **Abstract:** A compound of formula (1) and its salts and solvates are provided for the treatment or prophylaxis of hepatitis C virus infections. Methods of making and formulating compound (1) are provided.

WO 2008/005519 A3

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 24 April 2008

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/015553

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 A61K31/4353 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/063744 A (LEUVEN K U RES & DEV [BE]; PUERSTINGER GERHARD [AT]; GILEAD SCIENCES I) 14 July 2005 (2005-07-14) cited in the application pages 1,189; example 317	1-27
A	WO 2004/072243 A (ENANTA PHARMACEUTICALS INC [US]; MIAO ZENWEI [US]; SUN YING [US]; WU F) 26 August 2004 (2004-08-26) page 220; compound 186H	1-27

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2008	06/03/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BOURGHIDA, E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/015553

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/015553

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005063744 A	14-07-2005	AU 2004309390 A1	14-07-2005
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005286 A3

(51) International Patent Classification[7]: C07D 471/04, A61K 31/437, A61P 31/12 // (C07D 471/04, 235:00, 221:00)

(21) International Application Number: PCT/BE2003/000117

(22) International Filing Date: 3 July 2003 (03.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0215293.2 3 July 2002 (03.07.2002) GB
0313251.1 10 June 2003 (10.06.2003) GB

(71) Applicants *(for all designated States except US)*: **K.U.LEUVEN RESEARCH & DEVELOPMENT** [BE/BE]; Groot Begijnhof, Benedenstraat 59, B-3000 Leuven (BE). **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NEYTS, Johan** [BE/BE]; Heidebergstraat 278, B-3010 Kessel-Lo (BE). **PüRSTINGER, Gerhard** [AT/AT]; Roseggerstrasse 12, A-6020 Innsbruck (AT). **DE CLERCQ, Erik** [BE/BE]; Parklaan 9, B-3360 Lovenjoel (BE).

(74) Agents: **BIRD, William, E.** et al.; Bird Goën & Co, Klein Dalenstraat 42A, B-3020 Winksele (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

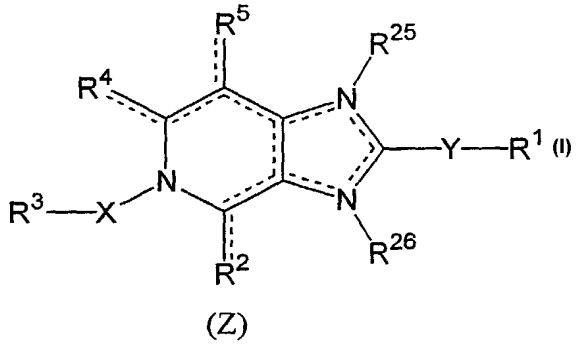
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 18 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/005286 A3

(54) Title: VIRAL INHIBITORS



(Z)

(57) Abstract: The present invention relates to a pharmaceutical composition for the treatment or prevention of viral infections comprising as an active principle at least one imidazo[4,5-c]pyridine derivative having the general formula (Z): (formula). The invention also relates to processes for the preparation of compounds according to the invention having above mentioned general formula and their use as a medicine or to treat or prevent viral infections.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/BE 03/00117

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P31/12 //(C07D471/04,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 158 440 A (ERBA FARMITALIA) 13 November 1985 (1985-11-13) page 4, line 3 -page 7; claims 1,9 ---	1
A	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine" retrieved from STN Database accession no. 110:165603 XP002265211 abstract & KHIMIKO-FARMATSEVTICHESKII ZHURNAL, vol. 23, no. 1, 1989, pages 56-9, --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2003	05/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/BE 03/00117

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HORVATH, A. ET AL.: "Preparation of sunstituted nitrogen-containing heterocyclic compounds" retrieved from STN Database accession no. 132:222537 XP002265212 RN=261379-92-4 & HU 78 019 A (HORVATH) 28 May 1999 (1999-05-28) ---	7
X	WO 99 27929 A (MERCK) 10 June 1999 (1999-06-10) example 4 (6) ---	7
X	WO 96 11192 A (SEARLE) 18 April 1996 (1996-04-18) page 207, example 358c ---	7
X	WO 96 12703 A (SEARLE) 2 May 1996 (1996-05-02) examples 11,18 ---	7
X	US 5 302 601 A (KHANNAL ISH K ET AL) 12 April 1994 (1994-04-12) examples ---	7
X	EP 0 344 414 A (SEARLE & CO) 6 December 1989 (1989-12-06) examples ---	7
X	WO 95 16687 A (ABBOTT LAB) 22 June 1995 (1995-06-22) examples ---	7
P,X	HISASHI AKAMATSU ET AL.: "New efficient route for solid-phase synthesis of benzimidazole derivatives" JOURNAL OF COMBINATORIAL CHEMISTRY., vol. 4, no. 5, 2002, pages 475-483, XP002265210 AMERICAN CHEMICAL SOCIETY, WASHINGTON., US ISSN: 1520-4766 pages 479, 480, compounds 15,16(21), 16(22) -----	7

INTERNATIONAL SEARCH REPORT

Inte onal application No.
PCT/BE 03/00117

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 7-14 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-14 (in part)

Present claims 7-14 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I described in page 19, line 15 - page 22, line 9.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/BE 03/00117

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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HU 78019	A	28-05-1999	HU	78019 A2	28-05-1999
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			NO	891058 A ,B,	15-09-1989
			NZ	228336 A	29-01-1992
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			ZA	8901926 A	30-05-1990
			PT	90208 A	10-11-1989
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			US	5019581 A	28-05-1991
			AT	112774 T	15-10-1994
			AU	3127089 A	14-09-1989
			CA	1337072 C	19-09-1995
			DE	68918755 D1	17-11-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna Application No
PCT/BE 03/00117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0344414 A		DE 68918755 T2	09-03-1995
		DK 121189 A	15-09-1989
		EP 0344414 A1	06-12-1989
		ES 2061753 T3	16-12-1994
		FI 891200 A ,B,	15-09-1989
		JP 1316378 A	21-12-1989
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		PH 26967 A	28-12-1992
		US 5227384 A	13-07-1993
		US 5302601 A	12-04-1994
		ZA 8901926 A	30-05-1990
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		BR 1100809 A3	23-11-1999
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		DK 734386 T3	27-05-2002
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		JP 9507474 T	29-07-1997
		PT 734386 T	31-07-2002
		WO 9516687 A1	22-06-1995

Corrected v-

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 626.PF	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/026606	International filing date *(day/month/year)* 26.07.2005	Priority date *(day/month/year)* 27.07.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D473/00 C07D471/04 C07D519/00 A61K31/52		
Applicant GILEAD SCIENCES, INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 19 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 43 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
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☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.05.2006	20.02.2007
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Frelon, Didier Telephone No. +49 30 25901-312

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-8, 11, 14-51, 54-56, 61, 68, 70-73, 76-83, 87-110, 112, 114-124	as originally filed
9, 10, 12, 13, 52, 53, 57-60, 62-67, 69, 74, 75, 84, 85, 111, 113	filed with telefax on 31.05.2006
86	filed with telefax on 13.11.2006

Claims, Pages

125-127, 129-135, 137-140	filed with telefax on 31.05.2006
128, 136	filed with telefax on 13.11.2006

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 62-69

because:

☒ the said international application, or the said claims Nos. 62-69 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-69
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-61
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

1. Amendments

Claims 1 to 55 on file repeat originally filed claims 1 to 55. Claims 56 to 69 on file repeat originally filed claims 64 to 68 and 70 to 78, respectively.

In reply to the WO-ISA of 01.03.2006, the Applicant has brought amendments within his replies received on 31.05.2006 and 13.11.2006 which consist essentially of the deletion of originally filed claims 56 to 63 and 69 (which was redundant with original claim 66). The remaining claims have been consecutively renumbered 1-69. The disputable term "isomers" has been deleted from claims 1, page 128 and 48, page 136.

In the description, formal amendments have been done:
- on pages 9, 10, 12, 13, 52, 59, 60, 62-67, 69, 74, 84 and 86, the expression "and the like" has been deleted.
- on pages 58, 59, 85, 111 and 113, "etc" has been similarly deleted. Note that most of such deletions have no effect when the affected sentence still contains a verb like "includes" or other enlarging expression like "but are not limited to" or "and so on".
- on page 75, the broadening introduction to the examples has been deleted.
- on said amended pages 53 and 57, the amendments are not clearly apparent.

It appears that the amendments have only excluded the subject-matter of original claims 56 to 63 which was considered to be non unitary. *The limitations of the searched scope have not been taken into account. The pending objections remain valid against the amended application.*

2. Scope limitation

The present claims 1-55, 61-69 relate to an extremely large number of possible compounds (claims 56-60 are directed to specific examples of the illustrations). In addition, it is noted that unspecific and/or open expressions like *aryl, heterocycle, aminoacid residue, ring, linking group, isomers* add to the lack of clarity and conciseness of the claims (see points 3.3.1ff, below). It is not said that a term like alkyl is not clear per se, but that the

combination of the numerous unspecific terms results in unclearly claimed subject-matters. The argument that recitation of subgenera may increase the complexity of the claims and reduce the conciseness cannot be accepted. Conciseness is not necessarily synonym of shorthand, abridgment, etc, particularly when the terms used for their theoretical conciseness do not cover meanings which are usually understood by the skilled person. Relevant repetitions may be necessary to set clarity. On the contrary, excessive "conciseness" is source of unclarity due to inconsistencies between the claims and the description where certain embodiments are said to be excluded (pages 17-20), partly referring to prior art documents (possibly said "incorporated by reference") or their family members. But the claims do not reflect this. Since it is the claims which define the matter for which protection is sought, if these exclusions correspond to a relevant prior art which is not come to the knowledge of the examining division, the claims could be considered to be anticipated by these compounds. Furthermore, if the said prior art was published before the priority date of the application, it may be necessary to contemplate this prior art for the assessment of inventive step.

The "formula" (A) in claim 1 or on page 3 is understood to be intended to cover a scope as large as possible but, as drafted, it goes against the requirements of the PCT for clarity and conciseness. A said Markush formulation can be a very useful and efficient way to claim a group of compounds, but it is not exempt to comply with clarity and conciseness requirements (Art. 5 and 6 PCT). It is understood that the Applicant expects that the full scope of the claimed subject-matter be searched, but this must be feasible and, for this purpose, the said scope must be clearly and concisely described. That is also why embodiments and illustrations by examples are useful to supply unspecific deficiencies. For instance, due to the dotted lines which should represent optional double bonds, the rests R^2, R^4 and R^5 are ill-defined since their definitions do comprise only monovalent groups which thus cannot link the imidazopyrimidine core twice. It would have been probably preferable to draw several figures, provided they comply with the unity requirements (Art. 3(4)(iii) PCT). A consequence is the impossiblity to determine the extent of the search because it cannot cover meaningfully an ill-defined claimed scope.

The first -relatively- clear and concise representation of a group of compounds could only be found with figure (A1), description page 28 [given that, since U is N, the rest R^5 is not optionally but *necessarily* absent - note that, if the nitrogen of the 4-position should be

quaternized, the definition of the claimed compounds would lack further clarity and conciseness because the definition of any necessary counterion would be absent] and with the prepared examples which are concrete forms of the invention: the search can only be made for a clear and concise subject-matter which is the first clear and concise subject-matter actually given by the Applicant in the specification. It was therefore certainly not arbitratry to focus the search as done since it followed the first indications made clear and concise by the Applicant.

Support and disclosure in the sense of Art. 6 and 5 PCT is to be found for only a very small proportion of the compounds claimed (see prepared examples 1-6 of pages 117-121) wherein (designation of figure (A1)):
- R^2, R^4 are H (R^5, R^{25} and R^{26} -designation of (A)- are necessarily absent due to the ring nitrogen valency),
- X represents CH_2,
- Y is a bond,
- R^1 is a (fluoro substituted) phenyl and
- R^3 represents a (trifluoromethyl or trifluoromethoxy substituted) phenyl or an isoxazole substituted by a (propoxy or chloro substituted) phenyl.

It will be also apparent to the skilled person that figure (A1), page 38, represents quite a large generalization of (a reasonable "penumbra around") the illustrations (see also points 3.3.1ff, below). The limitation of the search was consequently not arbitrary but guided by the subject-matter of the description which is consistent considering: YR^1 and R^3 = (hetero)ring and X = Alk, AlkO, AlkS or AlkN.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims (PCT Guidelines 9.19 and 9.23).

The search was necessarily restricted to those claimed compounds which appear to be supported and to a generalisation of their structural formulae, as described in formulae (A1) (said "fourth aspect" of the invention, page 27).

Re Item II

Due the presence of an intermediate document, the claimed priority date of 27.07.2004 had to be checked. It results that the priority is NOT valid when:

- R^1 is selected from C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino and C_4-C_{10} cycloalkynyl
- R^2 and R^4 are independently selected from haloalkyloxy (except OCF_3) and heterocycle (except 5- ot 6-membered heterocyclic),
- R^3 is selected from cycloalkyl (except C_3-C_{10} cycloalkyl), cycloalkenyl (except C_4-C_{10} cycloalkenyl), cycloalkynyl and heterocycle (except 5- ot 6-membered heterocyclic),
- R^5 is selected from haloalkyloxy (except OCF_3) and heterocycle (except 5- ot 6-membered heterocyclic),
- R^6 is selected from C_1-C_{18} alkylsulfoxide, C_1-C_{18} alkylsulfone, C_1-C_{18} haloalkyl, C_2-C_{18} haloalkenyl, C_2-C_{18} haloalkynyl, C_1-C_{18} haloalkoxy, C_1-C_{18} haloalkylthio, cyanoalkyl, -$C(O)OR^{18}$, arylsulfoxide, arylsulfone, arylsulfonamide and heterocycle (except 5- ot 6-membered heterocyclic),
- R^7 and R^8 are independently selected from heterocycle (except 5- ot 6-membered heterocyclic) and, when taken together with the nitrogen to which they are attached, they form a heterocycle (except 5- ot 6-membered heterocyclic),
- R^9 and R^{18} are independently selected from $CH_2CH(=O)R^{9a}$ and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl,
- R^{10} and R^{11} are independently selected from heterocycle (except 5- ot 6-membered heterocyclic) and an amino acid residue (when not linked through a carboxyl group thereof),
- R^{12} is an amino acid residue (when not linked through an amino group thereof),
- R^{15} and R^{16} are independently selected from arylalkyl (unsubstituted or substituted with $C(O)OR^{18}$) and an amino acid residue (when not linked through a carboxyl group thereof),
- R^{17} is selected from

(a) C_1-C_{18} alkylsuloxide, C_1-C_{18} alkylsulfone, C_1-C_{18} halogenated alkyl, C_2-C_{18} halogenated alkenyl, C_2-C_{18} halogenated alkynyl, C_1-C_{18} halogenated alkoxy, C_1-C_{18} halogenated alkylthio, CO_2R^{18}, haloalkyloxy (except OCF_3), arylsulfoxide, arylsulfone, arylsulfonamide, heterocycle (except 5- ot 6-membered heterocyclic) and

(b) M-Q- wherein M is a ring optionally substituted with a or more R^{19}, and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with one or more R^{19}.

- R^{19} is selected from
(c) sulfone, sulfonamide and sulfoxide,
(d) C_1-C_{18}, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl substituted by C_3-C_{10} cycloalkyl, C_4-C_{10} cycloalkenyl, C_4-C_{10} cycloalkynyl, aryl or heterocycle,
(e) C_1-C_{18}, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl wherein 1 or more methylene are replaced by 1 or more O (except C_1-$_{18}$ alkoxy), S (except C_1-$_{18}$ alkylthio), NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$,
(f) further substitutions of (c) and (e) by C_3-C_{10} cycloalkyl, C_4-C_{10} cycloalkenyl, C_4-C_{10} cycloalkynyl, aryl or heterocycle,
(g) heterocycle and C_3-C_{10} cycloalkyl, C_4-C_{10} cycloalkenyl, C_4-C_{10} cycloalkynyl, aryl or heterocycle further substituted with C_{1-6} alkyl, $C(O)OR^{12}$, =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$,
(h) $C(O)R^{18}$ and $C(S)R^{18}$ [wherein R^{18} is $NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group thereof, $CH_2CH(=O)R^{9a}$ and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl], $C(O)OR^{18}$ and $OC(O)R^{18}$ [with the full definition of R^{18}] and $C(O)N(R^{12})_2$ [except when one R^{12} is H and the other is C_{1-6} alkyl],
(i) to (k) further substitutions defined in the application on file
- R^{20} and R^{21} are independently heterocycle (except 5- ot 6-membered heterocyclic)
- R^{25} and R^{26} are independently heterocycle (except 5- ot 6-membered heterocyclic and pyridyl optionally substituted with 1 to 4 C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy and OH),
- R^{27} is arylC_{2-18} alkyl.

None of the specific compounds prepared in the application is disclosed within the priority document. Where the priority date is not valid, the intermediate document D10 is therefore relevant for the purposes of Rules 33.1c, 64.3 and 70.10 PCT (see section VI, certain documents), *i.e.* relevant in order to assess whether the claims satisfy the criteria set forth in Art. 33(1) PCT.

D10 may also be a relevant prior art with regard to inventive step (compounds of D10 are essentially different by the presence of a carbon atom in place of U) in a regional or national phase.

Re Item III

Claims 62-69 are directed to methods for treatment of the human or animal body by surgery or therapy and/or to diagnostic methods practised on the human or animal body. They relate to subject-matter considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of these claims on the question whether their subject-matter is industrially applicable, no unified criteria exist in the PCT Contracting States. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT). The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Cited documents

D1: WO 2004/005286
D2: EP 1 132 381
D3: EP 1 162 196
D4: WO 00/20400
D5: WO 95/02597
D6: GB 2 158 440

D7: DATABASE CA [Online]; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" Database accession no. 1989:165603

D8: WO 01/95910

D9: EP 1 386 923

D10: WO 2005/063744 (intermediate document)

2. Novelty

With the amendments (claims deletion) brought in answer to the previous written opinion, the objection of non unity has been overcome.

In the frame of the limited searched scope (see item I), compounds of formula (A) [*i.e.* (A1)] appear to be novel. These novel compounds, *i.e.* imidazo[4,5-d]pyrimidine derivatives (*i.e.* wherein U = N), are characterized by their substitution pattern such that the groups Y-R^1 and R^3 represent a ring (Y is a single bond).

3. Inventive step

3.1 The problem underlying the present application is to provide antiviral compounds. Compounds of D1 can be considered as the closest prior art in view of the part of the subject-matter which is entitled to the priority date. Compounds of D10 can be considered to be the closest prior art for the part of the subject-matter which is not entitled to the priority date.

3.2 The essential difference of the claimed subject-matter and the prior art is in both cases essentially to be seen in the replacement of a ring carbon atom by a nitrogen in place of U, *i.e.* in the condensed system wherein the ring carbon atom of the 7-position of the imidazopyridine is replaced by a nitrogen atom to form the present imidazopyrimidine. Such an exchange belongs to the general knowledge of bioisosterism of C and N as ring members. Document D3 which also belongs to the field of antiviral compounds illustrates the usual knowledge in drug design studies that carbon atom and nitrogen atom are commonly considered to be exchangeable unless a well known prejudice in the particular

domain of viral inhibitors would restrain the skilled person from proceeding with the C/N replacement. Similarly, X_8 of formula II in D4 and the ring members A, B, D and E in D8 illustrate this common knowledge. Even D2 which was cited against the novelty of the deleted claims confirms this very general knowledge with the ring members V and W which represent C or N. The Applicant did not bring the evidence that the present invention overcomes a known prejudice. The skilled person facing the problem mentioned above comes therefore directly to the solution of the present application.

The specification only describes assays and is silent about their concrete results. The qualification of the activity as excellent or of the toxicity as low lacks to point any reference which could give the significance of these qualities in order to substantiate the presence of an inventive step.

In order to show that the novel compounds are inventive, it must be clearly apparent that the differentiating feature is responsible for an unexpected effect. If this demonstration should be made by means of comparative tests, the compounds to be compare should be chosen such that they only differ by the diffentiating feature.

3.3 The Applicant's attention is drawn to the fact that, despite the limitations which were mandatory for the search (see item I), the claims do not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth for the claimed scope.

3.3.1 It is realized that the Applicant is entitled to claim all **obvious** modifications of what was concretely described and that alternative variations have to be supported by the description, *i.e.* a certain number of examples.

Open and non limitative (generalizing) expressions or terms like "*aryl, heterocycle, ring, linking group, aminoacid residue, etc*", derivatives thereof extend (irrealistically) the scope of the claims beyond what has actually been verified in the worked examples on file. For instance, the amino acid residue could be extremely different groups. Furthermore it is unclear whether an amino acid residue encompasses only the residue of a natural amino acid or whether it is also intended to cover a synthetic amino acid residue.

Undefined terms render the claims **obscure in scope** and do not allow to correctly and specifically circumscribe a scope where the invention applies and for which protection can actually be granted.

There should be no confusion between the clarity of certain terms (*i.e.* a straightforward comprehension which is not disputed) and the scope covered by these terms (*i.e.* an unlimited and therefore disputable extent) with the clarity and conciseness of the claims (Art. 6 PCT). Art. 6 PCT states unambiguously that the claims shall define the matter for which protection is sought. It is not said that they are defined "by reference to the description" but that they must be supported by the description. If a term in a claim actually includes a restriction, like here concerning the positional isomers, which is only mentioned in the specification, and if this restriction is not clear (even implicitly) from the text of the claim, the claim cannot be considered as fulfilling the requirements of clarity and conciseness.

The question is whether or not a technical effect is to be achieved by all the embodiments covered by the claims when this technical effect turns out to be the sole reason for the alleged inventiveness of these processes. A consequence is that broad expressions are objectionable under Art. 33(3) PCT. This is not only a question of terminology about the support for a scope and thus of "recasting" basis issues; the purpose is clearly a technical question whether the inventivity is credibly present over the whole claimed scope. Formal matters (clarity, support, etc) and obviousness are not "intermixed", although it cannot be denied that the corresponding objections are necessarily linked and cannot be artificially separated.

A legal principle is that the extent of a patent monopoly is justified by the technical contribution to the art. This principle which is applied in relation to the extent of the protection that is justified by reference to Art. 5 and 6 PCT also governs the decision which is required to be made under Art. 33(3) PCT, for everything falling within a valid claim has to be inventive. Judgement of inventive step depends on whether the specific technical purpose (a surprising or unexpected correlation between a structure and an activity) can be credibly achieved over the whole range claimed. A second legal principle is that any one who alleges a fact has the onus of proving this allegation by appropriate evidence. The fact that test results show that ***some*** of the claimed compounds are indeed active

cannot be regarded as sufficient evidence to lead to the inference that substantially ***all*** the claimed compounds possess this activity. The burden of proof that all the compounds claimed possess the alleged activity rests only upon the shoulders of the person alleging it.

3.3.2 The (given) examples (and particularly the tested ones) represent a relatively narrow illustration of the claimed scope (they have been already taken as a basis for the limitation of the search scope presently examined). It can be therefore questioned whether the regularly occuring groups in the examples form a necessary and essential characterisitic of the invention which should not be allowed to vary out of the ***reasonable*** extent of the usual equivalents and (bio)isosters of these variants, (especially keeping in mind that the difference with the prior art is relatively small, the effect (to be unexpected for an inventive step recognition) of which can be hindered by other unpredicted effects of larger structural variations of other variant groups that a skilled person cannot consider as obvious equivalents). In the present case the structural differences on passing from examples to compounds falling in the claims are far greater than the structural differences between compounds falling under the claims and compounds according to the prior art. Without any evidence of the contrary, the claimed scope do not represent a reasonable generalization of the very invention as shown by the examples.

Generalisations of concrete examples appear to be acceptable if they are not contradictory to the basis of qualitative or quantitative structure-activity-relationships (SAR) which says that for compounds with a certain chemical basic structure the known biological activity can *prima facie* be expected to be retained when making small structural modifications. These principles are well known to skilled persons in pharmacology and drug design and, if such principle would no longer apply at all, no generic formula in claims would be allowable at all for a pharmaceutical patent which then logically would have to be restricted to the concretely tested example(s).
It appears to be contradictory, on one hand to argue that, thanks to a very small structural modification on a position in a molecule, the known biological activity is surprisingly maintained or improved and, on the other hand, to claim a large number of structurally very different families of substituents through the above disputed terms (and their combinations) at various positions of the molecule under consideration.

Reasonable predictions of relations between chemical structures and biological activities

are in principle possible, but **there is a limit** beyond which no such prediction can be validly made. It is therefore necessary to fix limits to unspecific terms.

3.3.3 Open and too broad formulations may also lead to unacceptable **speculations** from the skilled people as to the very invention and its future aspects; it may even suggest that the claimed scope lacks any inventive merit and is not properly covered by the description and, particularly, the examples. Furthermore this would deprive any third party from a legitimate protection for a genuine invention in relation with an object which was neither described nor even foreseen but would have only been a hypothesis in the frame of the present invention.

When only some and not substantially all claimed compounds exhibit a particular technical effect, the conclusion has to be that the invention as broadly defined in the independent claim was not a solution to the technical problem of achieving the given technical effect (with the consequence that the alleged technical effect of some of the claimed compounds is to be disregarded when determining the objective problem underlying the invention and thus when assessing inventive step). In other words, a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the selected compounds. A general formulation, made up of many variables or groups defined by unlimited and/or vagues terms or non limitative expressions (including unspecific points of attachement), constitutes an excessive generalization encompassing forms which go far beyond what the skilled person, also taking into account physico-chemical and biological considerations, can regard as including obvious modifications, equivalents and/or (bio)isosterical values of substituents/of the examples given in the description.

There is indeed a great variety of structural possibilities which are claimed (and not yet explored by the Applicant), the *effect of which cannot be foreseen* having regard to the problem underlying the present application and, consequently, which are not solutions of the problem. Note that the Applicant's assertions as to the activity of the compounds is not questioned. They are believed to be active (point 3.2 above). The question is whether the claimed compounds develop any surprising effect which can serve as an objective basis to prove the presence of an inventive step.

3.3.4 The inventive step required by Art. 33(3) PCT can be acknowledged only for a well-defined scope embracing a specific domain thanks to a reasonable generalisation of the very invention, taking into account the extent of the illustration of the examples, the support of the specification, the closeness of the prior art, the reproducibility and the feasability of the invention. In other words, the protected scope should comprise only compounds, their variants and equivalents which solve the problem underlying the invention, (what is a prerequisite for the acknowledgement of an inventive step).

As chemical species can be precisely defined by the identity and the number of the atoms involved, it is necessary to specify the disputed expressions and terms by means of the incorporation of the definitions given in the specification.

Re Item VI

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2005063744	14.07.2055	21.12.2004	22.12.2003 02.01.2004 26.07.2004

Re Item VII

To meet the requirements of Rule 5.1(a) PCT, cited prior art documents should be identified in the description and the relevant background art disclosed therein should be briefly discussed. It is clear that, after amendments and clarifications, only relevant documents, *i.e.* closest prior art documents, are concerned.

Re Item VIII

1. Any expression or sentence which may also refer to an extent of protection beyond the actual invention is also objectionable (cf. "but are not limited to", "and so on"). The

insertion of such sentences and/or part of sentences would suggest that the subject-matter as presently disclosed does not cover properly the claimed scope. Any expression which can be interpreted as an unjustified extension of the claimed scope should be objected. The specification should be clear and sufficient by itself. A precautionary measure on the limits of the scope is therefore superfluous and even misleading as it finally prevents a proper definition of the invention and opens the way to speculations (of skilled persons) about the very inventive subject-matter. Consequently any element against clarity has to be deleted. In this sense, the expression "incorporated expressly herein by reference" is irrelevant and should be deleted. Note that, if the citations are "harmless" and do not affect the claimed scope, they are not necessary to a proper disclosure of the invention and there maintenance can be even misleading to the reader.

2. It is additionally noted that the terms and/or expressions such as "etc", "and the like" are unspecific. They cannot serve as a support for the invention and therefore should be deleted. Note that parts of the description which are obviously not related to the claimed subject-matter like definitions of groups which are not even mentioned in the claims should also be deleted.

The description refers to the exclusion of various compounds on page 20. The different scope of exclusion and the fact they need not be excluded in the description leads to an inconsistency with the claims.

3. References to methods of treatment or diagnostic methods as "embodiments" or as a further object or aspect of the invention should have been avoided since they are considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT. References to metabolites or isomers as further objects of the invention should have been avoided as well.

4. The reference to WO 00/204425 in the description is erroneous and should read WO 02/04425.

5. The reference to WO 2004/05286 (= D1) in claim 68 is considered to be irrelevant: (a) it refers to compounds which are not covered (as far as the given structure is clear) by the formula of the compounds (A1) of the searched invention which is the object of the present

Examination report, (b) the Applicant is reminded that whenever certain matter in a document is essential to satisfy the requirements of Art. 5 PCT, it should be expressly incorporated in the description because a patent specification should, regarding the essential features of the invention, be self-contained, *i.e.* capable of being understood without reference to any other document.

cyclopentyl, cycloheptyl, cyclooctyl, or a C_{7-10} polycyclic saturated hydrocarbon radical having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl.

"Alkenyl" means a hydrocarbon moiety with at least one site of double bond unsaturation where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain 1 to 3 carbon atoms, and each cyclic portion may contain 3 to 6 carbon atoms. A site of double bond unsaturation may be in a acyclic portion, a cyclic portion. In the instance of a moiety having a combination of acyclic and cyclic portions, there may be a site of double bond unsaturation in each of the portions. Within this definition, the term "cycloalkenyl" refers to the double bond unsaturated hydrocarbon moieties that are cyclic. Examples the term "alkenyl" include, but are not limited to, ethylene or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2), 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, and 1-cyclohex-3-enyl. The double bond optionally is in the cis or trans configuration.

"Alkynyl" means a hydrocarbon moiety with a least one site of triple bond unsaturation where the moiety may be acyclic, cyclic or a combination of acyclic and cyclic portions. The acyclic portion may contain contain 1 to 3 carbon atoms, and each cyclic portion may contain 7 or more carbon atoms. Within this definition, the term "cycloalkynl" refers to triple bond unsaturated hydrocarbon moieties that are cyclic. Examples of the term "alkynyl" include, but are not limited to, -CCH, -CH_2CCH, -CH_2CC-cyclohexyl, or -CH_2-cycloheptynyl.

The suffix "-ene" used in connection with alkyl, alkenyl and alkynyl groups refers to such groups with at least 2 sites of substitution. Such polyvalent hydrocarbon radicals include, but are not limited to, methylene (-CH_2-) 1,2-ethylene (-CH_2CH_2-), 1,3-propylene (-$CH_2CH_2CH_2$-), 1,4-butylene (-$CH_2CH_2CH_2CH_2$-), 1,2-ethylene (-CH=CH-), -CC-, propargyl (-CH_2CC-), and 4-pentynyl (-$CH_2CH_2CH_2$CCH-). Optionally, alkylene, alkenylene and alkynylene are substituted with O, S or N, generally meaning that O, S or N replace a carbon

atom and the valence appropriate number of carbon substituents (generally 1 or 2H). N in this case is generally R^{11}.

"Aryl" means an aromatic hydrocarbon containing 1 or more rings, generally 1, 2 or 3, with 4 to 6 carbon atoms in each, ordinarily 5 or 6 carbon atoms.

"Arylalkyl," "arylalkenyl" and "arylalkynyl" means an alkyl, alkenyl or alkynyl radical, respectively, in which one of the hydrogen atoms, typically a terminal or sp3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl.

As noted, carbocycles optionally are found as single rings or multiple ring systems. Ordinarily the hydrocarbons of the compounds of the formulas of this invention are single rings. Monocyclic carbocycles generally have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system.

If the number of carbon atoms is unspecified for a hydrocarbon, typically the number of carbon atoms will range from 1 to 18, except that the number of carbons typically will range from 2 to 18 for unsaturated hydrocarbons and from 6 to 10 for aryl.

"Heterocycle" or "heterocycle" means any 4, 5, 6, 7, 8 or 9 membered single or fused ring system containing one or more heteroatoms selected from the group consisting of O, N or S. Heterocycles optionally are entirely aromatic, entirely saturated, or contain 1 or more intra-ring sites of unsaturation, typically double bonds. Multiple heterocyclic rings (one or more of which contains a heteroatom) are bridged or spiro. Generally, the heterocyclic rings will be aromatic, and usually they are single rings. Examples of heterocycles include oxazacyloalkyl, morpholinyl, dioxacycloalkyl, thiacycloalkenyl, pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, furanyl, thienyl,

2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

Nitrogen containing heterocycles are bonded at nitrogen or a carbon, typically a carbon atom. These include, for example, position 1 of aziridine, 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, 1-piperidinyl, 2-pyrroline, 3-pyrroline, 2-imidazoline, 3-imidazoline, 9-carbazole, 4-morpholine, 9-alpha or ß-carboline, 2-isoindole, 2-pyrazoline and 3-pyrazoline, and by analogy, azetidine, pyrrole, pyrrolidine piperidine, piperazine, indole, pyrazoline, indoline, imidazole, imidazolidine, 1H-indazole and isoindoline. These and other N-containing heterocycles are well-known to those skilled in the art, and their linkage sites are a matter of discretion.

Sulfur containing heterocycles are bonded through carbon or sulfur. They include oxidized states such as -S(=O)(=O). In general, they are linked in the compounds of the formulas of this invention analogous to N-containing heterocycles.

"Alkoxy", "cycloalkoxy", "aryloxy", "arylalkyloxy", "oxy heterocycle", "thioalkyl", "thiocycloalkyl", "arylthio", and "arylalkylthio" means substituents wherein an alkyl, cycloalkyl, aryl, or arylalkyl, respectively, are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzyloxy, mercaptobenzyl.

"Halogen" means any atom selected from the group consisting of fluorine, chlorine, bromine and iodine.

Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

When a group is stated to be substituted with "one or more" of another group, this typically means 1 to 3 substituents, ordinarily 1, 2 or 3 substitutents.

Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among

other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state--any and all protonated forms of the compounds are intended to fall within the scope of the invention.

Amino Acids

"Amino-acid" refers to a radical derived from a molecule having the chemical formula H_2N–CHR[28]–COOH, wherein R[28] is a side group of a naturally-occurring or known synthetic amino-acid. The amino acids optionally are substituted with hydrocarbon typically of 1 to 8 carbons at one or more carboxyl or amino groups, whether those groups are on the side chain or are free after linking the amino acid to the remainder of the compound of this invention.

Optionally the amino acid residue is a hydrophobic residue such as mono- or di-alkyl or aryl amino acids, cycloalkylamino acids. Optionally, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included.

Generally, only one of any site in the parental molecule is substituted with an amino acid, although it is within the scope of this invention to introduce amino acids at more than one permitted site. In general, the alpha-amino or alpha-carboxyl group of the amino acid are bonded to the remainder of the molecule, i.e., carboxyl or amino groups in the amino acid side chains generally are not used

The compounds of this invention are useful as linkers, spacers or affinity (typically hydrophobic) moieties in preparing affinity absorption matrices. The compounds of the invention optionally are bound covalently to an insoluble matrix and used for affinity chromatography separations, depending on the nature of the groups of the compounds, for example compounds with pendant aryl groups are useful in making hydrophobic affinity columns.

They also are useful as linkers and spacers in preparing immobilized enzymes for process control, or in making immunoassay reagents. The compounds herein contain functional groups that are suitable as sites for cross-linking desired substances. For example, it is conventional to link affinity reagents such as hormones, peptides, antibodies, drugs, to insoluble substrates. These insolublized reagents are employed in known fashion to absorb binding partners for the affinity reagents from manufactured preparations, diagnostic samples and other impure mixtures. Similarly, immobilized enzymes are used to perform catalytic conversions with facile recovery of enzyme. Bifunctional compounds are commonly used to link analytes to detectable groups in preparing diagnostic reagents.

The compounds of this invention are labeled with detectable moieties such biotin, radioisotopes, enzymes for diagnostic purposes. Suitable techniques for accomplishing the labeling of the compounds of the formulas of this invention are well known and will be apparent to the artisan from consideration of this specification as a whole. For example, one suitable site for labeling is R^{17} or R^{19}.

More typically, however, the compounds of the invention are employed for the treatment or prophylaxis of viral infections such as yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus, but more particularly Flaviviral or Picornaviral infections, in particular, HCV and BVDV.

The therapeutic compound(s) of this invention are administered to a subject mammal (including a human) by any means well known in the art, i.e.

orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization. The therapeutically effective amount of the compound(s) is a Flaviviral or Picornaviral growth inhibiting amount. More preferably, it is a Flaviviral or Picornaviral replication inhibiting amount or a Flaviviral or Picornaviral enzyme inhibiting amount of the compounds of the formulas of this invention. This is believed to correspond to an amount which ensures a plasma level of between about 1μg/ml and 100 mg/ml, optionally of 10 mg/ml. This optionally is achieved by administration of a dosage of in the range of 0.001 mg to 60 mg, preferably 0.01 mg to 10 mg, preferably 0.1 mg to 1 mg per day per kg bodyweight for humans. These are starting points for determining the optimal dosage of the compound of this invention. The actual amount will depend upon many factors known to the artisan, including bioavailability of the compound, whether it contains a prodrug functionality, its metabolism and distribution in the subject and its potency, among others. It typically is necessary to determine the proper dosing in the clinical setting, and this is well within the skill of the ordinary artisan. The therapeutically effective amount of the compound(s) of this invention optionally are divided into several sub-units per day or are administered at daily or more than one day intervals, depending upon the pathologic condition to be treated, the patient's condition and the nature of the compound of this invention.

As is conventional in the art, the evaluation of a synergistic effect in a drug combination may be made by analyzing the quantification of the interactions between individual drugs, using the median effect principle described by Chou et al. in *Adv. Enzyme Reg.* (1984) 22:27 or tests such as, but not limited to, the isobologram method, as previously described by Elion et al. in *J. Biol. Chem.* (1954) 208:477-488 and by Baba et al. in *Antimicrob. Agents Chemother.* (1984) 25:515-517, using EC_{50} for calculating the fractional inhibitory concentration.

Suitable anti-viral agents for inclusion in combination antiviral compositions or for coadministration in a course of therapy include, for instance, interferon alpha, ribavirin, a compound falling within the scope of disclosure of EP 1162196, WO 03/010141, WO 03/007945, WO04/005286 and WO 03/010140, a

simultaneous, separate or sequential use in viral infection therapy, such as of HCV, BVDV and Coxsackie virus. Examples of such further therapeutic agents for use in combinations include agents that are effective for the treatment or prophylaxis of these infections, including interferon alpha, ribavirin, a compound faling within the scope of disclosure EP 1162196, WO 03/010141, WO 03/007945, WO04/005286 and WO 03/010140, a compound falling within the scope of disclosure WO 0/204425, and other patents or patent applications within their patent families or all the foregoing filings and/or an inhibitor of Flaviviral protease and/or one or more additional Flavivirus polymerase inhibitors.

When using a combined preparation of (a) and (b):

- the active ingredients (a) and (b) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- the therapeutically effective amount of the combined preparation of (a) and (b), especially for the treatment of viral infections in humans and other mammals, particularly is a Flaviviral or Picornaviral enzyme inhibiting amount. More particularly, it is a Flaviviral or Picornaviral replication inhibiting amount of derivative (a) and a Flaviviral or Picornaviral enzyme inhibiting amount of inhibitor (b). Still more particularly when the said Flaviviral or Picornaviral enzyme inhibitor (b) is a polymerase inhibitor, its effective amount is a polymerase inhibiting amount. When the said Flaviviral or Picornaviral enzyme inhibitor (b) is a protease inhibitor, its effective amount is a protease inhibiting amount.
- ingredients (a) and (b) may be administered simultaneously but it is also beneficial to administer them separately or sequentially, for instance within a relatively short period of time (e.g. within about 24 hours) in order to achieve their functional fusion in the body to be treated.

The invention also relates to the compounds of the formulas of this invention being used for inhibition of the proliferation of other viruses than BVDV, HCV or Coxsackie virus, particularly for the inhibition of other

flaviviruses or picornaviruses, with in particular yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus, and also for the inhibition of HIV and other retroviruses or lentiviruses.

More generally, the invention relates to the compounds of the formulas of this invention being useful as agents having biological activity (particularly antiviral activity) or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

Salts and Solvates

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms formed by the compounds of the compounds of this invention. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid.

The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

The compounds of this invention include the solvates formed with the compounds of this invention and their salts, such as for example hydrates, alcoholates. The compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the compounds of this invention with one or more amino acids as described above. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a compound of this invention. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

The compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na+, Li+, K+, Ca+2 and Mg+2. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in

association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li+, Na+, Ca+2 and Mg+2 and K+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, benzoic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, fumaric, tartaric, pyruvic, maleic, malonic, malic, salicylic (i.e. 2-hydroxybenzoic), *p*-aminosalicylic, isethionic, lactobionic, succinic oxalic and citric acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and *p*-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids,. C_1-C_6 alkylsulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic. Exemplary salts include mesylate and HCl.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX4+ (wherein X is C_1-C_4 alkyl). Physiologically acceptable salts

least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" contain undetectable levels of any other isomer.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), with asymmetric compounds bearing an acidic functionality, such as carboxylic acid and sulfonic acid.

The diastereomeric salts optionally are induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994). Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched

xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and Chiralpak™ AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane, modified with an alcohol such as ethanol, isopropanol. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990). "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

As used herein and unless otherwise stated, the term " enantiomer " means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and sterochemical forms, which the compounds of the formulas of this invention may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well.. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically

isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of the formulas of this invention may have at least one chiral center) of the basic molecular structure, as wel as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term "stereoisomerically pure" or "chirally pure" relates to compounds having a stereoisomeric excess of at least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantionierically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional

crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane, modified with an alcohol such as ethanol, isopropanol. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

The terms cis and trans are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents

on a ring moiety. The absolute stereochemical configuration of the compounds of formula (1) may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

Metabolites

The present invention also provides the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C14 or H3) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no antiviral activity of their own.

Formulations

The compounds of the invention optionally are formulated with conventional pharmaceutical carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers,

binders. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid.

Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the present invention. They may also include additives such as wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride), provided the same are consistent with pharmaceutical practice, i.e. carriers and additives which do not create permanent damage to mammals. The pharmaceutical compositions of the present invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the selected carrier material. Where appropriate, the other additives such as surface-active agents are prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with poylypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from I to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol - polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C_8-C_{22} alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Crop., Ridgewood, New Jersey, 1981), "Tensid-Taschenbucw', 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants, (Chemical Publishing Co., New York, 1981).

compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and mixtures thereof.

In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient,

e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Suitable methods for drug delivery include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and mixtures thereof.

Several active ingredients used in combination may not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated. Thus, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Exemplary Enumerated Compounds

Embodiments of the invention are named below in tabular format (Table 7). Each embodiment of Table 7 is depicted as a substituted nucleus (Sc) in which the nucleus is designated by a number and each substituent is designated in order by further numbers. Table 1 is a schedule of nuclei used in forming the embodiments of Table 7. Each nucleus (Sc) is given a number designation from Table 1, and this designation appears first in each embodiment name. Similarly, Tables 2, 3, 4, 5 and 6 list the selected substituents, again by number designation.

Accordingly, each named embodiment of Table 7 is depicted by a number designating the nucleus from Table 1. If the nucleus is of formula 1 (from Table

Exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations, and are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

General aspects of these exemplary methods are described below. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsecquent processes.

The terms "treated", "treating", "treatment", mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in

such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic sysnthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modification of the exemplified schemes and examples leads to various analogs of the specific exemplary materials produced above. The above citations describing suitable methods of organic synthesis are applicable to such modifications.

In the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid

chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. Such separations are desireable if addition reactions place substituents at both of the pyrimidine nitrogen atoms. Separation of these isomers is well within the skill of the artisan.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

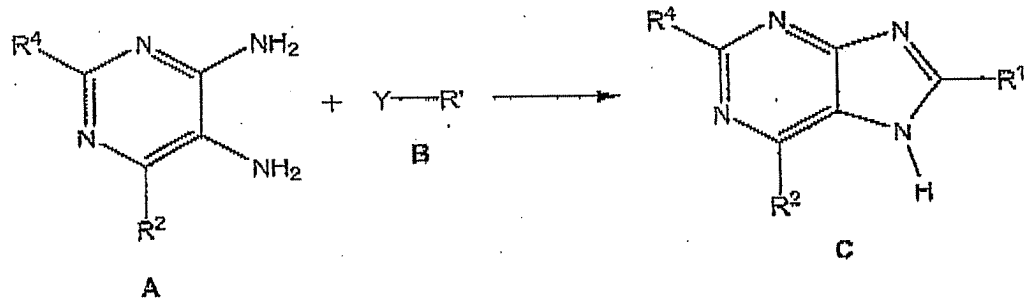
Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction. One skilled in the art will apply techniques most likely to achieve the desired separation.

A synthetic route to 5-benzyl-2-phenyl-5H-imidazo[4,5-d]pyrimidine and analogues is shown in Scheme A.

Compounds of the invention also are conveniently prepared by a two step process. First, a (substituted) 3,4-diaminopyrimidine (A) is reacted with B to give imidazo[4,5-d]pyrimidines C (Scheme 1). If Y is COOH, then the cyclization is carried out under acidic catalysis (preferably in polyphosphoric acid at a temperature between 90 and 200°C); other methods include reaction in 4N hydrochloric acid at reflux temperature or neat at a temperature between 90 and 180°C (for aliphatic carboxylic acids). In the case of acid-sensitive groups like alkoxy or thiophene, the reaction can be carried out in phosphorus oxychloride at a temperature between 70 and 120°C. Alternatively, reaction with aldehydes (Y = CHO) or their bisulfite adducts under oxidative conditions (nitrobenzene, DDQ, copper(II)acetate, O_2, sulfur) gives imidazo[4,5-d]pyrimidines C. Other methods are the reaction of (substituted) 3,4-diaminopyrimidines (A) with orthoesters (Y = $C(OR)_3$), anhydrides (Y = OCOOR) or acid halogenides (Y = COX).

Further methods for the preparation of the compounds of the invention are set forth in Schemes 1-5 below.

Scheme 1:

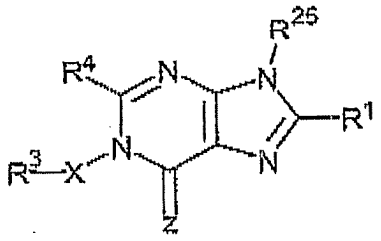


The imidazo[4,5-d]pyrimidines C are present in four tautomeric forms (1*H*, 3*H*, 4*H*, 6*H*).

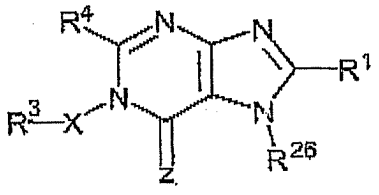
Substituents, for example R^2 and R^4, are introduced by two ways: i) by cylization of an appropiately substituted 3,4-diaminopyrimidine or ii) by

This mixture can be separated by column chromatography (silica gel, eluent: mixture of dichloromethane and methanol). The structures of the isolated components can then be assigned by NMR spectroscopy by single crystal x-ray analysis.

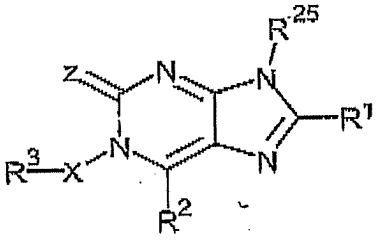
Alternatively, the crude reaction mixture can be recrystallized from an appropiate solvent (mixture), e.g. from a mixture of diisopropyl ether and ethyl acetate, to give the pure alkylated products.



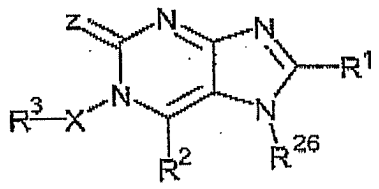
E



F



G



H

Compounds of general structure E, F, G and H can be prepared by alkylation (for example with (cyclo)alkylbromide or (cyclo)alkyliodide) of the corresponding compounds where Z=O, Z=S or Z=NR or their isomers. The resulting mixtures can be separated by column chromatography. The required starting materials are, for example, prepared from the corresponding chloro-analogues by nucleophilic substitution, or by ether cleavage of the corresponding alkoxy analogues.

chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. Such separations are desireable if addition reactions place substituents at both of the pyrimidine nitrogen atoms. Separation of these isomers is well within the skill of the artisan.

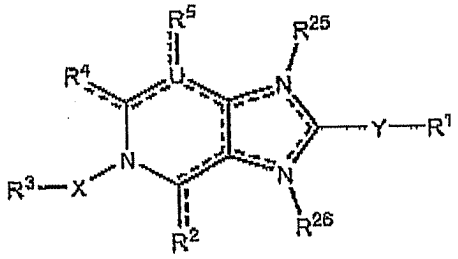
Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX).

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction. One skilled in the art will apply techniques most likely to achieve the desired separation.

A synthetic route to 5-benzyl-2-phenyl-5H-imidazo[4,5-d]pyrimidine and analogues is shown in Scheme A.

We Claim:

1. A compound of formula (A)



(A)

wherein:

the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

U is N;

R^1 is selected from hydrogen, aryl, heterocycle, C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl, C_1-C_{10} alkyl-amino, C_1-C_{10} dialkyl-amino, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or more R^6;

Y is selected from a single bond, O, S(O)m (where m is an integer from 0 to 2), NR^{11}, C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene, or C_{1-10} alkylene, C_{2-20} alkenylene or C_{2-10} alkynylene, wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR^{11};

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, $-NO_2$, $-NR^7R^8$, haloalkyloxy, haloalkyl, $-C(=O)R^9$, $-C(=S)R^9$, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-16} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, and heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from =O, =S, or $=NR^{27}$;

X is selected from C_1-C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, where each may include one or more heteroatoms selected from O, S, or NR^{11}, provided any such heteroatom is not adjacent to the N in the ring;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R^{10})-, or heterocycle, where each said substituent is optionally substituted with at least one R^{17}, provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO_2, -NR^7R^8, haloalkyloxy, haloalkyl, -C(=O)R^9, -C(=O)OR^9, -C(=S)R^9, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, and heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl, -CO_2R^{18}, NO_2, -NR^7R^8, C_{1-18} haloalkyl, C(=O)R^{18}, C(=S)R^{18}, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, and C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19};

R^7 and R^8 are independently selected from hydrogen, C_{1-10} alkyl, C_{1-10} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, heterocycle, -C(=O)R^{12}; -C(=S) R^{12}, an amino acid residue linked through a carboxyl group thereof, and the group formed when R^7 and R^8 are taken together with the nitrogen to form a heterocycle;

R^9 and R^{18} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{1-18} alkoxy, -$NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, and $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, and an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, arylalkyl (unsubstituted, or substituted with $C(O)OR^{18}$), C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, and an amino acid residue;

R^{17} is independently selected from the group consisting of (a) hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halogenated alkyl, C_{2-18} halogenated alkenyl, C_{2-18} halogenated alkynyl, C_{1-18} halogenated alkoxy, C_{1-18} halogenated alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, CO_2H, CO_2R^{18}, NO_2, NR^7R^8, haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, heterocycle, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle and C_{1-18} hydroxyalkyl, where each of said aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl, arylalkyloxy, arylalkylthio, heterocycle, or C_{1-18} hydroxyalkyl is optionally substituted with 1 or more R^{19}, and (b) M-Q- wherein M is a ring optionally substituted with 1 or more R^{19}, and Q is a bond or a linking group connecting M to R^2 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R^{19};

R^{19} is selected from

(a) H;

(b) NO_2, SH, $NR^{20}R^{21}$, OH, halogen and CN;

(c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle, and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, -C(=O)R^{12}, and -C(=S)R^{12};

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH;

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and arylC_{1-18} alkyl; and

salts, tautomers, polymorphs, isomers and solvates thereof.

2. The compound of claim 1 wherein R^1 is haloaryl, X is methylene, R^3 is heterocycle substituted with 1 or 2 R^{17}.

3. The compound of claim 1 wherein R^1 is an aryl or aromatic heterocycle substituted with 1 or 2 R^6.

4. The compound of claim 1 wherein R^3 is heterocycle.

5. The compound of claim 1 wherein YR^1 is haloaryl.

6. The compound of claim 5 wherein haloaryl is ortho-fluorophenyl.

7. The compound of claim 1 wherein R^3 is isoxazolyl substituted with 1 R^{17}.

8. The compound of claim 2 wherein R^{17} is aryl or an aromatic heterocycle which is substituted with 1, 2 or 3 R^{19}.

9. The compound of claim 1 wherein YR^1 is none of hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl.

10. The compound of claim 9 wherein YR^1 is not hydrogen or C_{1-6} alkyl.

11. The compound of claim 1 wherein R^{19} is trihalomethyl, trihalomethoxy, alkoxy or halogen.

12. The compound of claim 1 wherein R^1 is aryl or aromatic heterocyle substituted with 1, 2 or 3 R^6 wherein R^6 is halogen, C_{1-18} alkoxy; or C_{1-18} haloalkyl.

13. The compound of claim 12 wherein R^1 is phenyl substituted with 1, 2 or 3 halogens.

14. The compound of claim 13 wherein halogen is fluoro.

15. The compound of claim 1 wherein Y is a single bond, O, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene or one of said groups containing 1 to 3 heteroatoms selected from O, S or NR^{11}.

16. The compound of claim 15 wherein Y is $-O(CH_2)_{1-5}-$, $-(CH_2)_{1-5}-O-(CH_2)_{1-4}-$, $-S-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-S-(CH_2)_{1-4}-$, $-NR^{11}-(CH_2)_{1-5}-$, $-(CH_2)_{1-4}-NR^{11}-(CH_2)_{1-4}$ or C_{3-10} cycloalkylidene.

17. The compound of claim 15 wherein Y is $-OCH_2-$, $-CH_2O-$, C_{1-2} alkylene, C_{2-3} alkenylene, C_{2-3} alkynylene, O or a bond.

18. The compound of claim 15 wherein Y is a bond.

19. The compound of claim 1 wherein YR^1 is a single ring aromatic carbocycle or a heterocycle containing 1 or 2 N, S or O atoms in the ring.

20. The compound of claim 19 wherein the carbocycle or heterocycle contains 4 to 6 ring atoms.

21. The compound of claim 1 wherein YR^1 is halo- or halomethyl-substituted phenyl.

22. The compound of claim 1 wherein aryl or heteroaryl are substituted ortho or meta with halo- or halomethyl.

23. The compound of claim 1 wherein X is selected from the group consisting of alkylene, alkynylene or alkenylene and said hydrocarbons having an intrachain N, O or S heteroatom.

24. The compound of claim 1 wherein X is alkylene.

25. The compound of claim 23 wherein X is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-(CH_2)_{2-4}-O-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-S-(CH_2)_{2-4}-$, $-(CH_2)_{2-4}-NR^{10}-(CH_2)_{2-4}-$, C_{3-10} cycloalkylidene, C_{2-6} alkenylene and C_{2-6} alkynylene.

26. The compound of claim 1 wherein X is methylene.

27. The compound of claim 1 wherein R^5 is aryl or a heterocycle substituted with 0 to 3 R^{17}.

28. The compound of claim 27 wherein the heterocycle is an aromatic heterocycle.

29. The compound of claim 28 wherein the heterocycle contains 1, 2 or 3 N, S or O atoms in the ring, is linked to X through a ring carbon atom and contains 4 to 6 total ring atoms.

30. The compound of claim 29 wherein R^5 is isoxazolyl substituted with 1 to 3 R^{17}.

31. The compound of claim 1 wherein R^{17} is aryl or a heterocycle further substituted with 1 to 3 R^{19}.

32. The compound of claim 1 wherein M is aryl or aromatic heterocycle.

33. The compound of claim 1 wherein Q contains 0 to 20 atoms selected from C, O, S, N and H.

34. The compound of claim 1 wherein M is a cyclic group selected from R^{17}

35. The compound of claim 1 wherein R^{17} is selected from the group consisting of C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy; arylalkylthio; heterocycle; C_{1-18} hydroxyalkyl, each of said C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, arylalkyl; arylalkyloxy; arylalkylthio; heterocycle; and C_{1-18} hydroxyalkyl is unsubstituted or is substituted 1 or more R^{19}

36. The compound of claim 1 wherein R^{17} is selected from the group consisting of aryl and heterocycle, and where said aryl or heterocycle is optionally substituted with 1 or more R^{19}.

37. The compound of claim 1 wherein R^9 and R^{10} are H, OH or alkyl.

38. The compound of claim 1 wherein R^5 is H.

39. The compound of claim 1 wherein R^6 is halogen.

40. The compound of claim 1 wherein R^7, R^8, R^{10}, R^{11}, R^{15}, R^{16}, R^{20}, and R^{21} are independently H or C_{1-18} alkyl.

41. The compound of claim 1 wherein R^{12} is OH or alkyl.

42. The compound of claim 1 wherein R^{19} is selected from the group consisting of H; C_{1-18} alkyl; C_{2-18} alkenyl; C_{2-18} alkynyl; C_{1-18} alkoxy; alkenyloxy; alkynyloxy; C_{1-18} alkylthio; C_{3-10} cycloalkyl; C_{3-10} cycloalkenyl; C_{3-10} cycloalkynyl; halogen; OH; CN; cyanoalkyl; NO_2; $NR^{20}R^{21}$; haloalkyl; haloalkyloxy; $C(=O)R^{18}$; $C(=O)OR^{18}$; $OalkenylC(=O)OR^{18}$; $-OalkylC(=O)NR^{20}R^{21}$; aryl; heterocycle; $-OalkylOC(=O)R^{18}$, $C(=O)N(C_{1-6}$ alkyl), $N(H)S(O)(O)(C_{1-6}$ alkyl); arylalkyloxy; aryloxy; arylalkyloxy; and arylalkyl.

43. The compound of claim 42 wherein R^{19} is independently selected from the group consisting of halogen, $N(R^{20}R^{21})$, alkoxy, halo-substituted alkyl and halo-substituted alkoxy.

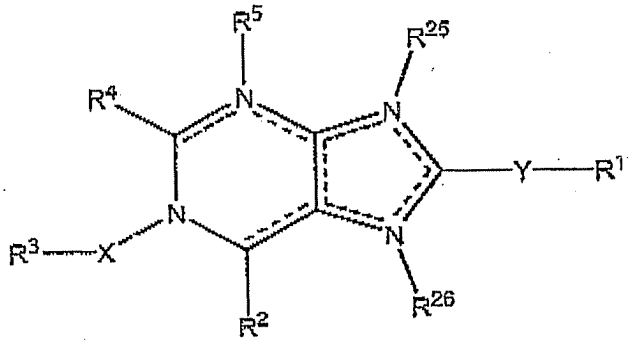
44. The compound of claim 1 wherein R^{25} and R^{26} are not present.

45. The compound of claim 1 which is not substituted at R^{25} but is substituted at R^{26}, and either R^2 or R^4 is selected from (=O), (=S), and (=NR^{27}).

46. The compound of claim 1 wherein haloalkyl or haloalkyloxy is $-CF_3$ or -OCF_3.

47. The compound of claim 1 wherein R^{19} is any individual, combination or subcombination of substituents (a) – (k).

48. A compound having the general formula (A),



(A)

wherein:

the dotted lines represent optional double bonds, provided that no two double bonds are adjacent to one another, and that the dotted lines represent at least 3, optionally 4 double bonds;

R^1 is selected from hydrogen, aryl, heterocycle (other than piperazinyl, piperidinyl, or either substituted with 1 or more R^6), C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl,

C_1-C_{10} alkyl-amino, C_1,C_{10} dialkyl-amino, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, and C_{4-10} cycloalkynyl, wherein each are optionally substituted with 1 or more R^6;

Y is selected from a single bond, O, S(O)m (where m is an integer from 0 to 2), NR^{11}; C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, or C_{1-10} alkylene, C_{2-20} alkenylene or C_{2-10} alkynylene wherein 1 to 3 methylene groups optionally are independently replaced by 1 to 3 heteroatoms selected from O, S or NR^{11}; provided, however, that YR^1 is not H;

R^2 and R^4 are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO_2, -NR^7R^8, haloalkyloxy, haloalkyl, -C(=O)R^9, -C(=S)R^9, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle, provided that when one of R^{25} or R^{26} is present, then either R^2 or R^4 is selected from (=O), (=S), and =NR^{27}; and further provided that not both of R^2 and R^4 is OH, SH, thio or oxo;

X is selected from C_1-C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene, where each may include one or more heteroatoms selected from O, S, or NR^{11}, provided any such heteroatom is not adjacent to the N in the ring;

R^3 is selected from aryl, aryloxy, arylthio, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl-N(R^{10})-, or heterocycle, where each said substituent may be optionally substituted with at least one R^{17}, provided that for cycloalkenyl the double bond is not adjacent to a nitrogen;

R^5 independently is absent or is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, halogen, -OH, -CN, -NO_2, -NR^7R^8, haloalkyloxy, haloalkyl, -C(=O)R^9, -C(=O)OR^9, -C(=S)R^9, SH, aryl, aryloxy, arylthio, arylalkyl, C_{1-18} hydroxyalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkylthio, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, or heterocycle;

R^6 is selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, C_{1-18} alkoxy, C_{1-18} alkylthio, C_{1-18} alkylsulfoxide, C_{1-18} alkylsulfone, C_{1-18} halo-alkyl, C_{2-18} halo-alkenyl, C_{2-18} halo-alkynyl, C_{1-18} halo-alkoxy, C_{1-18} halo-alkylthio, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{7-10} cycloalkynyl, halogen, OH, CN, cyanoalkyl,

$-CO_2R^{18}$, NO_2, $-NR^7R^8$, C_{1-18} haloalkyl, $C(=O)R^{18}$, $C(=S)R^{18}$, SH, aryl, aryloxy, arylthio, arylsulfoxide, arylsulfone, arylsulfonamide, aryl(C_{1-18})alkyl, aryl(C_{1-18})alkyloxy, aryl(C_{1-18})alkylthio, heterocycle, C_{1-18} hydroxyalkyl, where each may be optionally substituted with at least 1 R^{19};

R^7 and R^8 are independently selected from hydrogen, C_{1-18} alkyl, C_{1-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, heterocycle, $-C(=O)R^{12}$; $-C(=S)R^{12}$, an amino acid residue linked through a carboxyl group thereof, or where R^7 and R^8 together with the nitrogen form a heterocycle;

R^9 and R^{10} are independently selected from hydrogen, OH, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{1-18} alkoxy, $-NR^{15}R^{16}$, aryl, an amino acid residue linked through an amino group of the amino acid, $CH_2OCH(=O)R^{9a}$, or $CH_2OC(=O)OR^{9a}$ where R^{9a} is C_1-C_{12} alkyl, C_6-C_{20} aryl, C_6-C_{20} alkylaryl or C_6-C_{20} aralkyl;

R^{10} and R^{11} are independently selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, aryl, $-C(=O)R^{12}$, heterocycle, or an amino acid residue;

R^{12} is selected from the group consisting of hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{15} and R^{16} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, or an amino acid residue;

R^{17} is independently M-Q- wherein M is a ring optionally substituted with 1 or more R^{19}, and Q is a bond or a linking group connecting M to R^3 having 1 to 10 atoms selected from C and optionally 1 or more O, N or S atoms and optionally substituted with 1 or more R^{19};

R^{19} is selected from

(a) H;

(b) NO_2, SH, $NR^{20}R^{21}$, OH, halogen and CN;

(c) Sulfone, sulfonamide and sulfoxide;

(d) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl;

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, or $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH; and

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl, and

salts, tautomers, polymorphs, isomers and solvates thereof.

49. The compound of claim 48 wherein Y is a single bond, and R^1 is aryl or aromatic heterocycle which is unsubstituted or substituted with one or more R^6.

50. The compound of claim 48 wherein X is C_1-C_{10} alkylene, C_{2-10} alkenylene or C_{2-10} alkynylene.

51. The compound of claim 48 wherein R^3 is heterocyle.

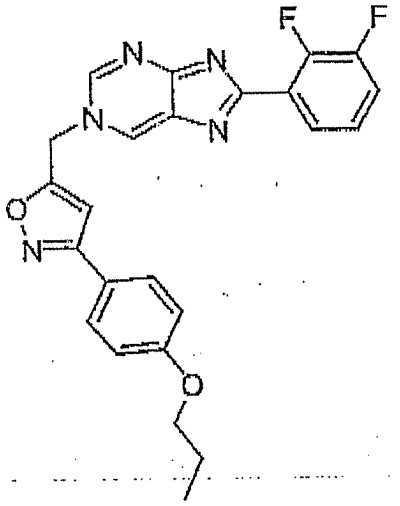
52. The compound of claim 48 wherein R^3 is heterocycle substituted with R^{17} where Q is a bond and M is aryl substituted with 1 or 2 R^{19}.

53. The compound of claim 48 wherein Y is a single bond, and R^1 is phenyl.

54. The compound of claim 48 wherein R^3 is isoxazole substituted with R^{17} where Q is a bond and M is aryl substituted with 1 or 2 R^{19}.

55. The compound of claim 48 wherein R^3 is isoxazole substituted with R^{17} where Q is a bond and M is phenyl substituted with 1 or 2 R^{19}.

56. A compound having the structure

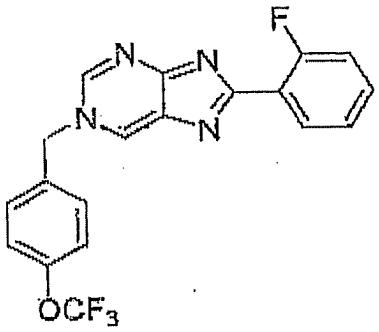


and its salts, tautomers, polymorphs and solvates.

57. 8-(2-Fluorophenyl)-1-[(4-trifluoromethyl)phenylmethyl]-1*H*-purine and its salts, tautomers, polymorphs and solvates.

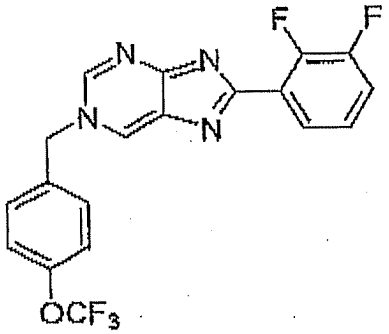
58. 1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-8-(2,3-difluorophenyl)-1H-purine and its salts, tautomers, polymorphs and solvates.

59. The compound



and its salts, tautomers, polymorphs and solvates.

60. A compound of the structure



and its salts, tautomers, polymorphs and solvates.

61. A composition comprising a pharmaceutically acceptable excipient and a compound of claims 1, 48, and 64-70.

62. A method comprising administering to a subject in need of treatment or prophylaxis of a viral infection an antivirally effective amount of a composition of claim 61.

63. The method of claim 62, wherein the viral infection is an HCV infection.

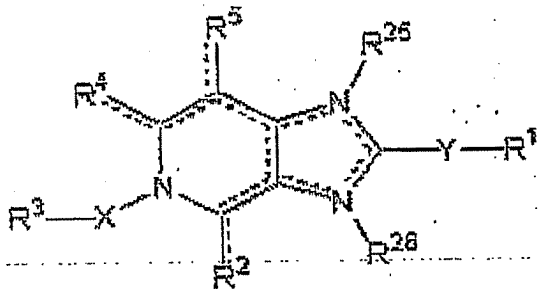
64. The method of claim 63 further comprising administering at least one additional antiviral therapy to the subject.

65. The method of claim 64 wherein the additional therapy is is selected from the group consisting of an interferon alpha and ribavirin.

66. A method of screening antiviral compounds which comprises providing a compound of claims 1 or 48 and determining the anti-viral activity of said compound.

67. The method of claim 66 wherein said anti-viral activity is determined by the activity of said compound against one or more viruses belonging to the family of the Flaviviridae and/or of the Picornaviridae.

68. A method for structure-activity determination of analogues of compounds of WO 2004/005286 having the general structure



wherein the R, X and Y groups are defined in WO 2004/005286, comprising

(A) preparing an analogue of a compound falling within the scope of WO 2004/005286 wherein C_γ is replaced by N; and

(B) determining the anti-HCV activity of the compound of step (A).

69. The method of claim 68 wherein the substituent is located at R^3, R^2, R^4, R^{2b} and/or R^1.

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle, and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$, and $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH;

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and arylC_{1-18} alkyl; and

salts, tautomers, polymorphs, stereoisomers and solvates thereof.

2. The compound of claim 1 wherein R^1 is haloaryl, X is methylene, R^3 is heterocycle substituted with 1 or 2 R^{17}.

3. The compound of claim 1 wherein R^1 is an aryl or aromatic heterocycle substituted with 1 or 2 R^6.

(e) C_{1-18} alkyl, C_{2-18} alkenyl and C_{2-18} alkynyl wherein 1 or more methylene are replaced by 1 or more O, S, NR^{20}, $C(O)NR^{20}R^{21}$, $OC(O)R^{12}$, $C(O)OR^{12}$ or $N(R^{20})C(O)$;

(f) Substituents c), d) or e) substituted further by C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl or heterocycle;

(g) C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, C_{4-10} cycloalkynyl, aryl and heterocycle, or said groups substituted with C_{1-6} alkyl, $C(O)OR^{12}$ =O, halogen, CN, $C(O)NR^{20}R^{21}$, $C(O)R^{18}$ or $OC(O)R^{18}$;

(h) $C(O)R^{18}$, $C(O)OR^{18}$, $OC(O)R^{18}$, $C(S)R^{18}$ and $C(O)N(R^{12})_2$;

(i) Substituents d) or e) substituted with =O, CN, halogen, $C(O)R^{18}$, $C(O)NR^{20}R^{21}$, $OC(O)R^{18}$, heterocycle and heterocycle substituted with C_1-C_6 alkyl, $C(O)OR^{12}$, =O, CN, halogen, $OC(O)R^{18}$ or $C(O)NR^{20}R^{21}$;

(j) Substituents c) substituted further with C_{1-18} alkyl; and

(k) Substituents f) or g) substituted further with C_{1-18} alkyl, =O, $NR^{20}R^{21}$, CN, C_{1-18} alkoxy, heterocycle, C_{1-18} haloalkyl, heterocyclealkyl or halogen;

R^{20} and R^{21} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, aryl, heterocycle, C_{3-10} cycloalkyl, C_{4-10} cycloalkenyl, $-C(=O)R^{12}$; or $-C(=S)R^{12}$;

R^{25} and R^{26} are independently not present or are selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, aryl and heterocycle, where each is optionally independently substituted with 1 to 4 of C_{1-6} alkyl, C_{1-6} alkoxy, halo, CH_2OH, benzyloxy, and OH; and

R^{27} is selected from hydrogen, C_{1-18} alkyl, C_{3-10} cycloalkyl, (C_{3-10} cycloalkyl)-C_{1-6} alkyl, aryl, and aryl C_{1-18} alkyl, and

salts, tautomers, polymorphs, stereoisomers and solvates thereof.

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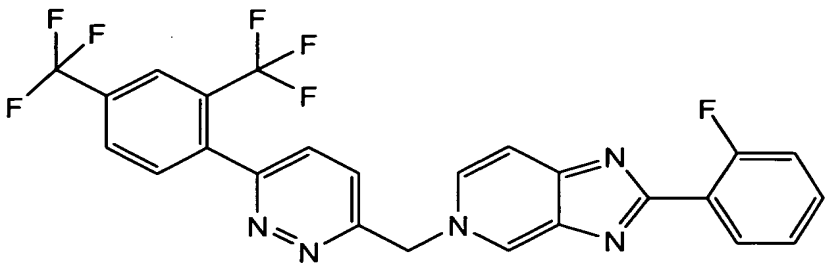
(54) Title: CRYSTALLINE PYRIDAZINE COMPOUND



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(57) Abstract: A crystalline compound of formula (1) and its salts and solvates are provided for the treatment or prophylaxis of hepatitis C virus infections (1) Methods of making and formulating crystalline compound (1) are provided.

WO 2009/009001 A1

CRYSTALLINE PYRIDAZINE COMPOUND

Background of the Invention

The hepatitis C virus is an enveloped, single-stranded, positive sense RNA virus in the family *Flaviviridae*. HCV mainly replicates within hepatocytes in the liver. Circulating HCV particles bind to receptors on the surfaces of hepatocytes and subsequently enter the cells. Once inside the hepatocyte, HCV utilizes the intracellular machinery necessary to accomplish its own replication. Lindenbach, B. Nature 436(7053):932-8 (2005). The HCV genome is translated to produce a single protein of around 3011 amino acids. This "polyprotein" is then proteolytically processed by viral and cellular proteases to produce three structural (virion-associated) and seven nonstructural (NS) proteins.

HCV encodes two proteases, the NS2 cysteine autoprotease and the NS3-4A serine protease. The NS proteins then recruit the viral genome into an RNA replication complex, which is associated with rearranged cytoplasmic membranes. RNA replication takes places via the viral RNA-dependent RNA polymerase of NS5B, which produces a negative-strand RNA intermediate. The negative strand RNA then serves as a template for the production of new positive-strand viral genomes. Nascent genomes can then be translated, further replicated, or packaged within new virus particles. New virus particles presumably bud into the secretory pathway and are released at the cell surface.

HCV has a high rate of replication with approximately one trillion particles produced each day in an infected individual. Due to lack of proofreading by the HCV RNA polymerase, HCV also has an exceptionally high mutation rate, a factor that may help it elude the host's immune response.

Based on genetic differences between HCV isolates, the hepatitis C virus species is classified into six genotypes (1-6) with several subtypes within each genotype. Subtypes are further broken down into quasispecies based on their genetic diversity. The preponderance and distribution of HCV genotypes varies globally. For example, in North America genotype 1a predominates followed by 1, 2a, 2b, and 3a. In Europe genotype 1 is predominant followed by 2a, 2b, 2c, and 3a. Genotypes 4 and 5 are found almost exclusively in Africa. Genotype is clinically important in determining potential response to interferon-based therapy and the required duration of such therapy. Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes (2, 3, 5 and 6). Duration of standard interferon-based therapy for genotypes 1 and 4 is 48 weeks, whereas treatment for genotypes 2 and 3 is completed in 24 weeks.

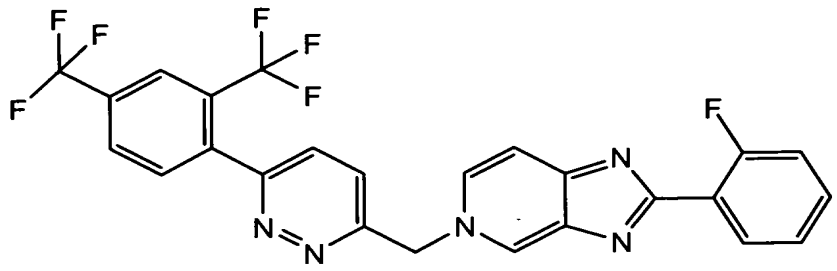
The World Health Organization estimates that world-wide 170 - 200 million people (3% of the world's population) are chronically infected with HCV. Approximately 75% of these individuals are chronically infected with detectable HCV RNA in their plasma. These chronic carriers are at risk of developing cirrhosis and/or liver cancer. In studies with a 7-16 years follow-up, 7-16 % of the patients developed cirrhosis, 0.7-1.3% developed hepatocellular carcinoma and 1.3-3.7% died of liver-related disease.

The only treatment option available today is the use of interferon α-2 (or its pegylated form) either alone or combined with ribavirin. However, sustained response is only observed in about 40% of the patients and treatment

is associated with serious adverse effects. There is thus an urgent need for potent and selective inhibitors of HCV.

Relevant disclosures include U.S. Patent Nos. 4,914,108; 4,988,707; 4,990,518; 5,137,896; 5,208,242; 5,227,384; 5,302,601; 5,374,638; 5,405,964; 5,438,063; 5,486,525; 6,479,508; and U.S. Patent Publication No. US2003/0108862 A1, Canadian Patent No. 2423800 A1, German Patent Nos. 4211474 A1, 4236026, 4309969, 4318813, European Patent Nos. EP 0 138 552 A2, EP 0 706 795 A2, EP 1 132 381 A1, Great Britain Patent No. 2158440 A, PCT Patent Publication Nos. WO 00/20416, WO 00/39127, WO 00/40583, WO 03/007945 A1, WO 03/010140 A2, WO 03/010141 A2, WO 93/02080, WO 93/14072, WO 96/11192, WO 96/12703, WO 99/27929, PCT-US2004/43112, PCT-BE2003/000117, PCT-US2005/26606, Akamatsu, et al., "New Efficient Route for Solid-Phase Synthesis of Benzimidazole Derivatives", 4:475-483, *J. COMB. CHEM.*, 2002, Baginski SG et al., Proc. Natl. Acad. Sci. U.S.A. 2000 Jul 5;97(14):7981-6). Cleve et al., "Derivate des Imidazo[4.5-b]- und Imidazo[4.5-c]pyridins", 747:158-171, *JUSTUS LIEBIGS ANNALEN DER CHEMICA*, 1971, Kiyama, et al., "Synthesis and Evaluation of Novel Nonpeptide Angiotensin II Receptor Antagonists: Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent", 43(3):450-60, *CHEM PHARM BULL*, 1995, Mederski et al., "Synthesis and Structural Assignment of Some N-substituted Imidazopyridine Derivatives", 48(48):10549-58, *TETRAHEDRON*, 1992, Yutilov et al., 23(1):56-9, *KHIMIKO-FARMATSEVTICHESKII ZHURNAL*, 1989. In addition, see WO 05/063744.

The compound of formula (1) is the subject of WO 08/005519.



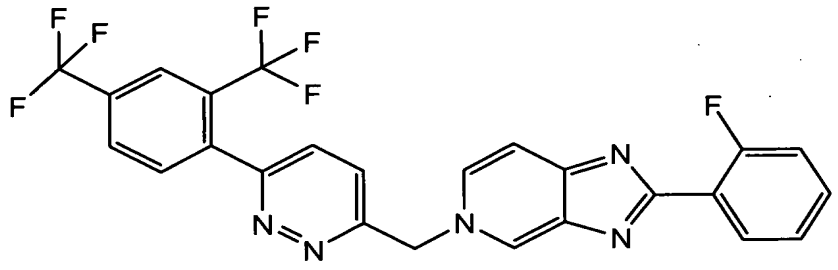
(1)

Compound (1) as produced by the process of WO 05/063744 is substantially or entirely amorphous. It is believed to be a hydrate (hereafter "amorphous" compound (1)).

It is an object of this invention to provide compound (1) in crystalline form.

Summary of the Invention

In accordance with achieving the foregoing objects of this invention, a crystalline compound is provided having formula (1)

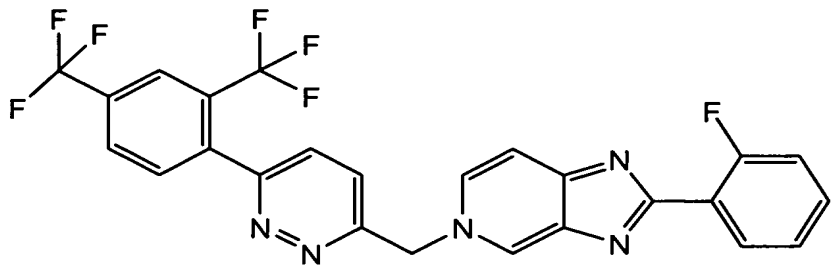


(1)

and its salts, which is substantially free of amorphous compound (1) .

In an embodiment, the crystalline compound (1) is the free base substantially free of amorphous compound (1) and any other crystal form of compound (1).

Another embodiment of this invention is a method for making crystalline compound (1)



(1)

comprising crystallizing compound (1) from crystallization solvent and controlling the amount of water in the crystallization solvent.

In another embodiment, a composition is provided that comprises crystalline free base compound (1) which is substantially free of the chloride salt of compound (1).

Crystalline compound (1) is useful in a method for therapy or prophylaxis of HCV infection comprising administering to a subject a therapeutic or prophylactic dose of crystalline compound (1). Another embodiment comprises the use of crystalline compound (1) for the manufacture of a medicament for the prevention or treatment of an HCV infection in a mammal (more specifically a human).

Another embodiment of this invention relates to pharmaceutical compositions of the crystalline formula (1) compound comprising at least one pharmaceutically acceptable excipient. In one embodiment the compound of formula (1) is formulated with an organic acid and optionally formulated into a

pharmaceutical dosage form such as a capsule. In another embodiment, crystalline compound (1) is micronized and formulated as a suspension.

Crystalline compound (1) or the pharmaceutical compositions of this invention are employed in the treatment or prophylaxis of hepatitis C.

Crystalline compound (1) exhibits improvements in pharmacological features and cost advantages, in particular improved purity, storage stability and manufacturing reproducibility. A particular advantage is its higher melting point as compared to the amorphous form.

Other features of this invention, including novel intermediates and product compositions, will be apparent from consideration of this application as a whole.

Figures

Figure 1 depicts an X-ray powder diffraction (XRPD) pattern obtained for crystalline compound (1) reference standard obtained by the method of example 1.

Figure 2 depicts another X-ray powder diffraction pattern obtained for crystalline compound (1).

Figure 3 is an X-ray powder diffraction pattern obtained for the amorphous form of compound (1) Research Lot 6, obtained by the method of Example 1a in WO 08/005519.

Figure 4 illustrates a DSC thermogram obtained for crystalline compound (1) reference standard, 1°C/min scan, obtained by the method of Example 1 below.

Figure 5 shows a DSC thermogram obtained for the amorphous form of compound (1) Research Lot 6, 5°C/min scan, obtained by the method of Example 1a in WO 08/005519.

Detailed Description of the Invention

Crystalline compound (1) is defined as a solid comprising compound (1) in which the constituent molecules are packed in a regularly ordered repeating pattern extending in all three spatial dimensions. Identification of crystallinity is readily accomplished in a number of ways known to those skilled in the art. Microscopic examination of the test composition often will reveal the presence of regular shapes, suggesting ordered internal structure. In the case of the crystal embodiment produced in example 1, the regular shape generally is rod or needle-like.

XRPD is another method for identifying crystalline compound (1). The regularly ordered structure of constituent molecules in a crystal diffracts

incident x-rays in a distinct pattern depicted as a spectrum of peaks. This pattern of peaks for crystalline compound (1) is shown in Figures 1 and 2. On the other hand, Figure 3 depicts an XRPD for substantially amorphous compound (1), which lacks distinct peaks. While the XRPD peaks for crystalline compound (1) may vary in intensity the same general pattern will be present in replicate x-ray diffraction analysis.

Crystalline compound (1) exhibits an XRPD dominant peak(s) at about 17 degrees theta 20, ordinarily 17.4 and 17.5. By "about" applicants mean within the typical variation in measurement of XRDP peaks. Such variations may result from the use of different instruments, instrument settings, batches of product, post-crystallization processing such as micronization or milling, and with varying sample preparation methods. In general, "about" means $\pm$ 0.5 degree theta 20. An example of this sort of variation can be seen by comparing Figures 1 and 2. In particular, peak intensity (e.g., at about 30) may vary due to crystal orientation effects.

Illustrative examples of other dominant peaks for crystalline compound (1) are at about 8, 10, 13, 16, 19 and 24 degrees theta 20, ordinarily 8.4, 10.0, 13.5, 15.7, 16.8, 16.9, 18.8 and 24.4. Any one or more of these peaks (but especially, 8, 10, 15.7, 16.7 and 16.9, with or without the peaks at about 17, are suitably employed to define the XRDP for crystalline compound (1).

The identification of a crystal form of compound (1) need not require the presence of any one or more of the dominant peaks seen in Figures 1 or 2. Rather, the presence or absence of dominant peaks ordinarily is taken into account with other diagnostic characteristics (e.g., DSC thermogram) to identify a candidate as crystalline compound (1).

Crystalline compound (1) also is characterized by DSC thermogram, which reveals an endothermic onset at about 235°C in differential scanning calorimetry profile. Typically, some variation in this measurement also will be encountered (usually, $\pm$ 1 - 3°C).

Crystalline compound (1) also is characterized by its heat of fusion (DH_f) of about 81 J/g (42 KJ/mole).

Crystalline compound (1) is made by a process comprising dissolving compound (1) in solvent and forming crystals therefrom. Typical solvents for use herein are ethyl acetate, isopropyl alcohol or a cosolvent containing ethyl acetate and isopropyl alcohol. Other suitable solvents are obtained from the solubility map in McConville, F.X. "Pilot Plant Real Book" (2002) which plots the dielectric constant and Hildebrand solubility parameter for a variety of solvents.

Solvents close to ethyl alcohol and isopropyl alcohol on the map (dielectric 2.5-20 and Hildebrand 15-24) are ethyl ether, isobutyl acetate, butyl acetate, anisole, chlorobenzene, chloroform, methyl acetate, THF, dichloromethane, dichloroethane, 1,2-dichlorobenzeke, methylisobutylketone, methylethylketone, cyclohexanone, acetone, 1-butanol, 2-methoxyethanol, isobutanol, 2-butanol, cyclohexanol, isoamyl alcohol, pyridine, methyl formate, 1-pentanol, and/or 2-butoxyethanol.

Some of these solvents would not be preferred due to toxicity issues, but this could be overcome by careful solvent removal from the product. It will be within the skill of the ordinary artisan to conduct laboratory screening to determine suitability of a candidate solvent for the preparation of crystalline

compound (1). Combinations of these solvents also fall within the scope of the invention.

A key finding facilitating the preparation of crystalline compound (1) is that the water content of the crystallization solvent must be controlled in order to obtain and/or optimize the production of crystalline product. For example, when using ethyl acetate as solvent, the upper limit on water content is about 0.6% to 0.9% by weight.

An additional consideration with regard to water content is its use to remove other forms of compound (1) that are less soluble than the crystalline free base in liquid lipophilic pharmaceutical carriers. For example the chloride salt of compound (1) is less soluble than the free base in the fatty acid solutions employed as carriers herein. In sufficiently large amounts such salts produce an undesirable haze in the pharmaceutical product. The final synthetic step of example 1 produces a mixture of free base together with minor amounts of the chloride salt. The haze-producing chloride salt is removed by first dissolving the product in a solvent containing a relatively high amount of water (about 3% - 10%) at alkaline pH. Refluxing in this solvent assures that there is enough water to back convert the chloride salt to the free base. Thereafter, the crystalline free base is crystallized from this solvent. This process optionally is repeated with decreasing water concentrations to gradually remove the chloride salt from the product. The final step is then accomplished with low water content (usually less than about 0.9% water) in order to crystallize the free base substantially free of the amorphous compound (1). In general, haze in the pharmaceutical preparation is not encountered when the chloride content in the final product is ordinarily less than about 100 ppm. The amounts of water employed will vary depending upon the concentration of contaminating

chloride salt and other experimental variables determinable by the skilled artisan. In summary, the water content of the crystallization solvent is controlled, both to convert chloride (or other relatively water soluble salts of compound (1)) and to avoid generation of amorphous compound (1).

The amount of permitted water for each function will vary depending upon the solvent or solvents employed for crystallization, the concentration of compound (1), the temperature of the crystallization step, the time of crystallization, the tolerable amount of amorphous compound (1), and other variables. Hence, it will be incumbent upon the artisan to determine the optimal water level for obtaining the desired results, usually by conducting a typical variable matrix study. The lowest water concentration for avoiding generation of the amorphous compound (1) is more a matter of practical economics. For example, 0.05% water by weight is acceptable.

In general, the final crystallization step is conducted in substantially anhydrous solvent. Substantially anhydrous solvent is defined as solvent containing a sufficiently small amount of water that the resulting product contains crystalline compound (1) and is substantially free of amorphous compound (1), typically less than about 40%, ordinarily less than about 30, 20, 10, 5, 3, 2 or 1% by weight of amorphous compound (1) in the total of all forms of compound (1) in the product composition.

In general, substantially anhydrous solvent will about 0.5% - 0.9% water by weight of the crystallization solvent. However, more water can be present if the desired product is permitted to contain the greater proportions of amorphous compound (1). However, it is optimal if the compound (1) composition is free of detectable amorphous compound (1).

The water content is controlled by any manner results in the proper amount of water in the crystallization step concerned. When formation of amorphous compound (1) is to be avoided, suitable techniques for minimizing or reducing the amount of water include adding drying agents and/or azeotropically removing water. It is most convenient to remove water during reflux dissolution of compound (1) just prior to crystallization. Of course, control of water content includes adding water as well, as will typically be the case during steps to convert the chloride salt.

Amorphous compound (1) optionally is used as starting material for crystallization (form conversion). Alternatively, crystallization is conducted directly from the final reaction products without an intermediate recovery of amorphous compound (1). The crystallization typically is conducted by providing or dissolving compound (1) in solvent or solvent mixture at reflux (sufficient to dissolve compound (1), about 1 to 5 hours), followed by cooling to about 18-23°C over 4 – 8 hours, then optionally agitated for about 8 to 20 hours at about 18-23°C. Agitation is optional but increases the rate of crystallization. Reflux is not critical since all that is necessary is that compound (1) be placed in solution. However, refluxing compound (1) has the advantage of rapidly dissolving compound (1) and azeotropically removing water at the same time. Water is controlled before crystallization starts or during crystallization, or both, although in general it is best to reduce water below the desired limit before any compound (1) can precipitate as the amorphous polymorph.

Generation of amorphous material is optimized by using relatively longer crystallization times, higher temperatures and lower concentrations of compound (1). Determining the various optimal crystallization process parameters are well within the skill of the ordinary artisan.

An embodiment herein is a composition made by the process of combining crystalline compound (1) with a pharmaceutically acceptable excipient and forming a pharmaceutical dosage form such as a tablet or capsule. The resulting product need not contain crystalline compound (1). While it is expected that dosage forms made from crystalline compound (1) will contain only compound (1) in crystalline form. However, in some embodiments the crystalline compound (1) is an intermediate for dissolution in the carrier or excipient.

The crystalline compound (1) of this invention is administered to a subject mammal (including a human) by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization in a therapeutically effective amount, i.e., an HCV-inhibiting amount or an HCV-replication inhibiting amount. This amount is believed to be an amount that ensures a plasma level of about 100 nM, 3 times the protein-adjusted EC90. This ordinarily is expected to be achieved by daily oral administration of about 0.5 – about 5 mg/kg, typically about 0.7 to 2.2 mg/kg, most ordinarily about 1.2 mg/kg bodyweight for humans.

The optimal dosage of the compound of this invention will depend upon many factors known to the artisan, including bioavailability of the compound in a given formulation, the metabolism and distribution of the compound in the subject, the fasted or fed state of the subject, selection of carriers and excipients in the formulation, and other factors. Proper dosing typically is determined in the preclinical and clinical settings, and is well within the skill of the ordinary artisan. The therapeutically effective amount of the compound of this invention optionally is divided into several sub-units per day or is administered daily or

in more than one day intervals, depending upon the nature of the infection, the patient's general condition and the formulation of the compound of this invention. Generally, the compound is administered twice daily.

The compound of this invention is employed in concert with other agents effective against HCV infections. They optionally are administered separately in a course of therapy, or are combined with compound (1) in a unitary dosage form such as tablet, iv solution or capsule. Such other agents include, for instance, interferon-alpha, ribavirin, and/or compounds falling within the disclosures of EP1162196, WO 03/010141, WO 03/007945, WO 00/204425 and/or WO 03/010140 (and other filings within their patent families). Other agents for administration in a course of therapy with the compound of this invention include compounds now in clinical trials, in particular HCV protease inhibitors such as VX-950 (Vertex Pharmaceuticals), SCH 5030347 (Schering Plough) and BILN-2061 (Boehringer Ingelheim), nucleoside HCV inhibitors such as NM283, NM107 (both Idenix/Novartis) and R1626 (Hoffmann-LaRoche), and non-nucleoside HCV inhibitors including HCV-086 and -796 (both ViroPharma/Wyeth). Supplementary antiviral agents are used in conventional amounts. If the efficacy of the compound of this invention and the supplementary compound are additive then the amounts of each active agent optionally are commensurately reduced, and more so if the agents act synergistically. In general, however, the agents are used in their ordinary active amounts in unitary combination compositions.

Co-administered agents generally are formulated into unitary compositions with the compound of this invention so long as they are chemically compatible and are intended to be administered by the same route.

If not, then they optionally are provided in the form of a medical kit or package containing the two agents in separate repositories or compartments.

The compound of this invention typically is provided as the free base, but also optionally is prepared as a salt. Salts typically are prepared by acid addition of organic and/or inorganic acids to the free base. Examples include (1) inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and sulfamic acids; or (2) organic acids such as acetic, propanoic, hydroxyacetic, benzoic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, fumaric, tartaric, pyruvic, maleic, malonic, malic, salicylic (e.g. 2-hydroxybenzoic), p-aminosalicylic, isethionic, lactobionic, succinic, oxalic and citric acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, C1-C6 alkylsulfonic, benzenesulfonic, p-toluenesulfonic, and cyclohexanesulfamic acids. Typical salts are the chloride, sulfate, bisulfate, mesylate, besylate, esylate, phosphate, oxalate, maleate, succinate, citrate, malonate, and/or fumarate salts. Also included within the scope of this invention are the salts of the compound of this invention with one or more amino acids, typically naturally-occurring amino acids such as one of the amino acids found in proteins. The acidic counterion desirably is physiologically innocuous and non-toxic or otherwise pharmaceutically acceptable, unless the salt is being used as an intermediate in preparation of the compounds whereupon toxicity is not relevant. Ordinarily, compound (1) will be administered as the free base, but suitable salts include mesylate (methanesulfonic acid) and HCl.

The compound of this invention includes the solvates formed with the compound of this invention or their salts, such as for example hydrates, alcoholates and the like.

The pharmaceutical compound of this invention optionally is formulated with conventional pharmaceutical carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (2005) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose and/or organic acids such as oleic acid or stearic acid.

The term "pharmaceutically acceptable carrier" as used herein means any material or substance formulated with the active ingredient in order to facilitate its preparation and/or its application or dissemination to the site to be treated. Suitable pharmaceutical carriers for use in the compositions of this invention are well known to those skilled in the art. They include additives such as wetting agents, dispersing agents, adhesives, emulsifying agents, solvents, glidants, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), and isotonic agents (such as sugars or sodium chloride), provided that the same are consistent with pharmaceutical practice, i.e. they are not toxic to mammals.

The pharmaceutical compositions of the present invention are prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients in a one-step or multi-step procedure, with the selected carrier material and, where appropriate, other additives such as surface-active agents. Compositions containing the compound of this invention

formulated into microspheres (usually having a diameter of about 1 to 10 gm) are useful as controlled or sustained release formulations.

In one optional formulation, compound (1) is comminuted to a finely divided form, typically to an average particle size at any point within the range of about 1 - 20 microns. The product of example 1 is rods or needles and exhibits a range of crystal length, typically about 25 – 40 microns. These optionally are micronized in a Jet mill-00 at about 60-80 psi to obtain particles of about 3-4 microns and having surface area of about 7-8 square meters/g. However, the starting crystal sizes will vary from lot to lot and the degree of micronization is a matter of choice. Accordingly, micronized crystalline compound (1) is simply defined as crystal or amorphous compound (1) that has been subject to a micronization process such as the exemplary one described here. Neither the size nor surface area of the resulting particles is critical. The micronized compound (1) is suspended in aqueous solution, optionally aided by a suspending agent, emulsifiers and/or surfactant as further described below.

Typically, the pharmaceutical formulation is a solubilized form of compound (1) where crystalline compound (1) is dissolved in an appropriate solvent or solubilizing agent, or combinations thereof. Crystalline compound (1) is solubilized in a pharmaceutically acceptable excipient for administration therapeutically or prophylactically.

Suitable solutions of compound (1) for pharmaceutical preparations include water together with various organic acids (typically C4 – C24) usually fatty acids like capric, oleic, lauric, capric, palmitic and/or myristic acid. The fatty acids are optionally saturated or unsaturated, or mixtures thereof. In addition, polyethylene glycols (PEGs) and/or short, medium, or long chain

mono, di, or triglycerides are employed supplementary to, or in place of, the organic acids. Pegylated short, medium or long chain fatty acids optionally also are used in the same fashion.

The most common organic acids are the carboxylic acids whose acidity is associated with the carboxyl group -COOH. Sulfonic acids, containing the group OSO_3H, are relatively stronger acids for use herein. In general, the acid desirably contains a lipophilic domain. Mono- or di-carboxylic acids are suitable.

Suitable surface-active agents optionally are used with any of the formulations of this invention (any one or more of the following agents, typically any one of them). Such agents also are known as emulgents or emulsifiers, and are useful in the pharmaceutical compositions of the present invention. They are non-ionic, cationic and/or anionic materials having suitable emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C_{10}-C_{22}), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable from coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-

earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alcoholamine salts of dodecylbenzene sulphonic acid or dibutyl-naphthalenesulphonic acid or a naphthalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphoshatidyl -choline and their mixtures. Aqueous emulsions with such agents are within the scope of this invention.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with poylypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups.

Such compounds usually contain from I to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol -polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C8 - C22 alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl and oleyl) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose is found in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Crop., Ridgewood, New Jersey, 1981), "Tensid-Taschenbucw", 2nd ed. (Hanser Verlag, Vienna, 1981) and "Encyclopedia of Surfactants," (Chemical Publishing Co., New York, 1981).

The compound of this invention is administered by any route appropriate to the condition to be treated, such as oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient, but is generally oral.

Formulations of the compound of this invention for oral administration usually are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granular form; as a solution or suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The compound of this invention optionally is presented as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets are prepared by compressing in a suitable machine the compound of the invention in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active and/or dispersing agent. Molded tablets typically are made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

The formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the compound is employed with a paraffinic or a water-miscible ointment base. Alternatively, the compound is formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or

more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention is constituted from known ingredients in a known manner. While this phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties

required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered by aerosol or powder inhalers, of which numerous examples are available. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations

containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

The compound of this invention optionally is formulated into controlled release compositions in which the release of the compound is controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of the invention compound. Controlled release compositions are prepared in accord with known methods, many of which involve formulating the active compound with one or more polymer carriers such a polyester, polyamino acid, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymer, methylcellulose, carboxymethylcellulose and/or protamine sulfate. The rate of drug release and duration of action optionally is controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Also suitable are colloid drug delivery systems such as liposomes, microspheres, microemulsions,

nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition, e.g., tablets, may require protective coatings.

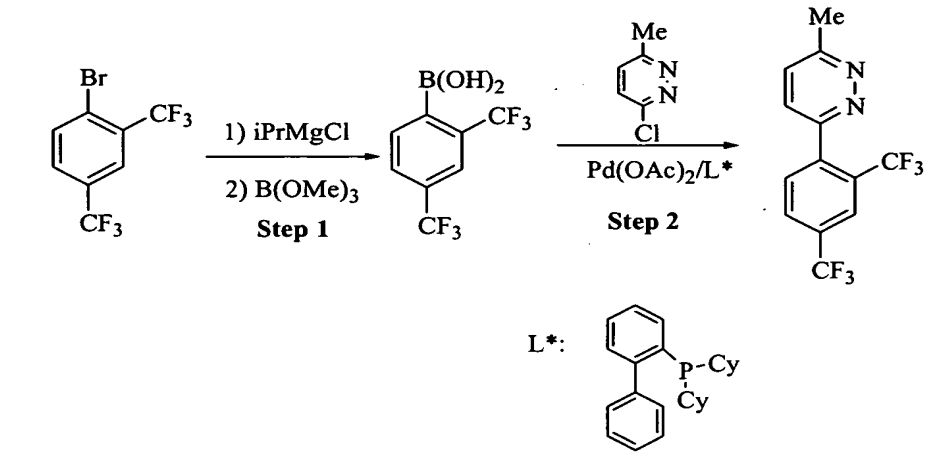
The invention will be more fully appreciated by reference to the following examples, which are to be considered merely illustrative and not limiting the scope of the invention.

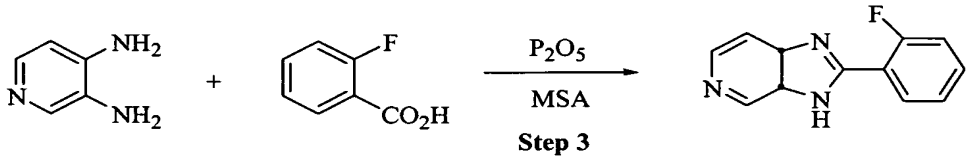
Composition percentages are by weight unless otherwise apparent from the context.

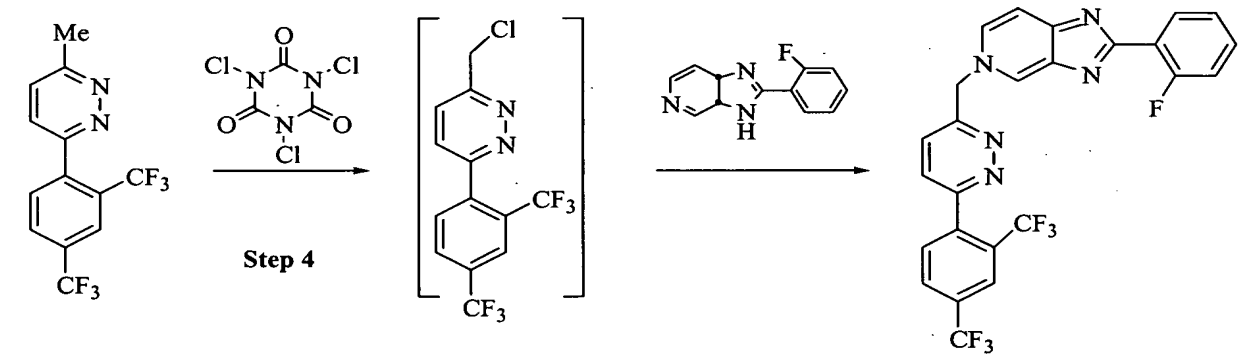
Example 1

Synthesis of Crystalline 5-((6-(2,4-Bis(trifluoromethyl)phenyl]pyridazin-3-yl)methyl)-2-(2-fluorophenyl)-5*H*-imidazo[4,5-*c*]pyridine

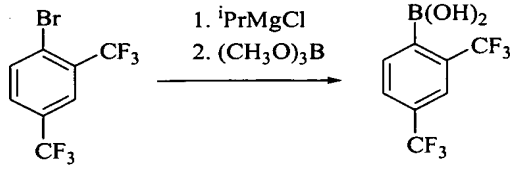
Scheme 1







Step 1



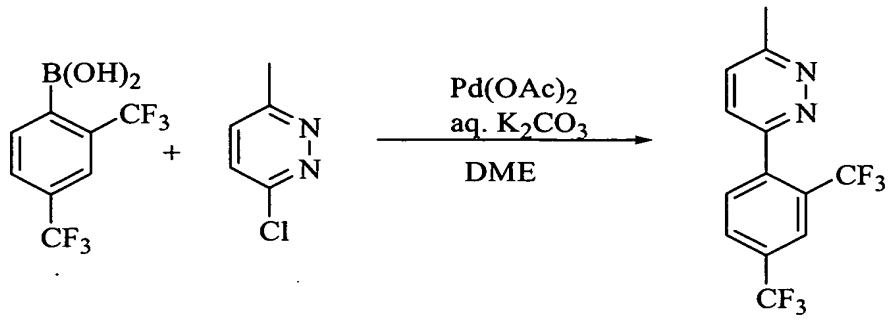
To a reactor, containing 2,4-bis(trifluoromethyl)bromobenzene (1.00 eq) and tetrahydrofuran (THF), was charged Isopropyl magnesium chloride

(^{i}PrMgCl) (2 M in THF, 1.14 eq) while maintaining the content at -10°C. The mixture was agitated at -10°C until the reaction was completed by HPLC analysis. The resultant mixture was transferred to the second reactor, containing trimethyl borate (2.26 eq) and THF held at a temperature of -10°C. The reaction was then monitored by HPLC until 1,3-bis(trifluoromethyl)benzene was not more than 2%. Aq. HCl (aqueous hydrochloric acid), prepared from water and concentrated 37% hydrochloric acid (HCl) were then added to quench the reaction while maintaining the content at not more than 25°C. After agitating the content for 1-2 h and settling for ca. 30 minutes, the layers were separated. The organic layer was washed with brine solution mixed with water and then concentrated under vacuum. Heptane was charged and the content was further concentrated under vacuum. The operations were repeated one more time. Heptane was then charged and the resultant slurry is cooled to 3°C, and agitated at the temperature for 4-6 h.

The product was filtered, washed with heptane twice and dried under vacuum at a maximum of 40°C.

Material	M.W.	v/w Ratio	w/w Ratio	Mole Ratio
2,4-Bis(trifluoromethyl)-bromobenzene	293.00	—	1.00	1.00
Heptanes	100.21	13.20	9.00	—
Hydrochloric acid, concentrated (37%)	36.50	0.42	0.50	—
Isopropyl magnesium chloride (2 M in Tetrahydrofuran)	102.85	1.95	1.90	1.14
Sodium Chloride (NaCl)	58.11	—	0.60	—
Tetrahydrofuran (THF)	72.11	4.50	4.00	—
Trimethyl borate	103.91	0.86	0.80	2.26
Water	18.02	8.90	8.90	—

Step 2



Compound 2a

3-Chloro-6-methylpyridazine (1.00 eq), 2-(dicyclohexylphosphino)biphenyl (0.05 eq), 2,4-bis(trifluoromethyl)phenylboronic acid (1.85 eq), 1,2-dimethoxyethane and aqueous potassium carbonate solution were all charged into a reactor. After degassing three times with nitrogen, palladium acetate (0.025 eq) was charged and the content is heated and agitated under reflux until the reaction was deemed complete.

The reaction mixture was cooled to 22°C. Heptane was charged, followed by addition of Celite. After agitating for ca. 30 minutes at 22°C, the mixture was filtered into the first reactor, rinsing forward with a mixture of 1,2-dimethoxyethane and Heptanes. The layers of the filtrate are separated.

To the organic layer was charged borane trimethylamine complex (0.03 eq), water, and acetic acid. The resultant mixture with a pH at maximum 4 was agitated for 1-2 h at 22°C and then refluxed at ca. 80°C for 2-3 h. After cooling back to 22°C, the mixture was adjusted to pH 10-11 with addition of 5% aq. sodium hydroxide while maintaining the content at 22°C and then agitated for 1-2 h. The mixture was filtered and the layers were separated. The aq. layer was disposed of and the organic layer was filtered through ZetaCarbon cartridges

into the in-process cleaned first reactor, rinsing forward with 1,2-dimethoxyethane through the carbon cartridges.

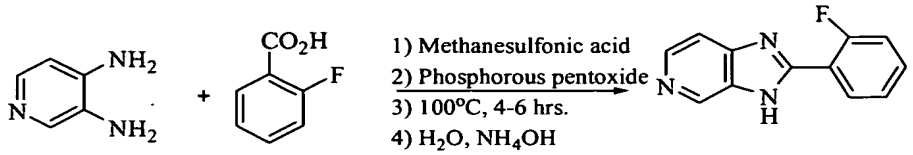
The filtrate was concentrated under vacuum with a maximum jacket setting of 60°C. Heptane was charged and the contents were further concentrated under vacuum with a maximum jacket setting of 60°C. Additional Heptane was charged to the concentrate and the 1,2-dimethoxyethane (DME) content (maximum 0.5%) of the mixture was checked by NMR. After adjusting to 85°C and agitating for ca. 1 h, the mixture was polished filtered hot through a filter into the second reactor.

The filtrate in the second reactor was adjusted to reflux and then agitated for 1 h. With ramp cooling and moderate agitation, the mixture is cooled from reflux to 0 to 6°C over a period of minimum 4 h and then agitated at 0 to 6°C for 1 h.

The product was filtered, washed with ambient temperature Heptanes and dried under vacuum at a maximum of 40°C until loss on drying is maximum 1%.

Materials	**M.W.**	**w/w Ratio**	**Mole Ratio**	**v/w Ratio**
2,4-Bis(trifluoromethyl)phenyl-boronic acid	257.92	4.00	1.85	—
Borane trimethylamine complex	72.92	0.018	0.03	—
3-Chloro-6-methylpyridazine	128.56	1.00	1.00	—
Diatomaceous earth (celite)	N/A	0.30	—	—
Di(cyclohexyl)phosphinobiphenyl	350.49	0.14	0.05	—
1,2-Dimethoxyethane	90.12	12.00	—	13.80
Drinking water	18.02	3.75	—	3.75
Glacial acetic acid	60.05	0.05	0.10	—
Heptanes	100.21	20.40	—	29.80
Palladium (II) acetate	224.49	0.044	0.025	—
Potassium carbonate,	138.21	2.15	2.00	—
Sodium hydroxide, 5% solution	40.00	—	—	—

Step 3



3,4-Diaminopyridine MW = 109.13 | 2-Fluorobenzoic Acid MW = 140.11 | Core (2) MW = 213.2

To a reactor was charged methanesulfonic acid, followed by phosphorus pentoxide (1.00 eq) in portions while maintaining the content at 23°C. 3,4-Diaminopyridine (1.00 eq) was charged in portions while maintaining the content at 20 to a maximum of 50°C. 2-Fluorobenzoic acid (1.09 eq) was then charged. The mixture was heated to 100°C and the reaction was monitored by HPLC until completion.

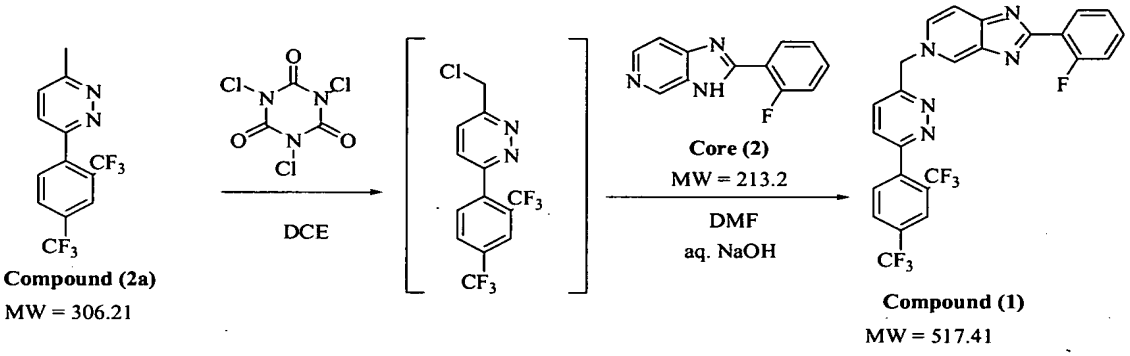
The content was adjusted to 10°C and water was charged while maintaining the content at a maximum of 25°C. After agitating the mixture at this temperature for 1 h, it was filtered into a second reactor.

To the filtrate in the second reactor was charged 27% ammonium hydroxide until the pH was in between 6.0-6.5. The content temperature was kept at a maximum of 30°C. The resultant thin slurry was agitated at 22°C for a minimum of 1 h and 27 % ammonium hydroxide was further charged, until the pH was between 8.0-9.3. The slurry was further agitated at 22°C for a minimum of 2 h.

The product was filtered, washed with water twice, and dried at a maximum of 60°C under vacuum, until the water content is not more than 1%. If necessary, the product is milled to remove large lumps.

Materials	M.W.	w/w Ratio	Mole Ratio	v/w Ratio
Ammonium hydroxide, 27%	35.05	—	—	—
3,4-Diaminopyridine	109.13	1.00	1.00	—
Drinking water	18.02	24.00	—	24.00
2-Fluorobenzoic acid	140.11	1.40	1.09	—
Methanesulfonic acid	96.10	7.00	—	4.70
Phosphorous pentoxide	141.94	1.30	1.00	—

Step 4



To a reactor is charged compound 2a (1.24 eq), methylene chloride and trichloroisocyanuric acid (0.491 eq). The mixture wxas adjusted to reflux and agitated under reflux until the reaction is complete.

The reaction mixture was cooled to 22°C and celite was charged. After agitating for minimum of 30 minutes, the mixture was filtered into and rinsed forward with methylene chloride 3 times into the second reactor. The filter cake was disposed of. To the filtrate in the second reactor was charged 3% aq. sodium hydroxide whilst maintaining the contents at 22°C. The mixture was agitated for 1-2 h and the layers were separated. The bottom organic layer was transferred to the in-process cleaned first reactor and concentrated under vacuum with a maximum jacket temperature of 45°C. Methylene chloride was

charged and the mixture was polish filtered to the in-process cleaned second reactor.

The filtrate was concentrated under vacuum with a maximum jacket temperature of 45°C. Dimethylformamide (DMF) was charged and the contents are further concentrated. The mixture was adjusted to 22°C and DMF was charged, followed by compound core 2 (1.00 eq) and 10% aq. sodium hydroxide while maintaining the content at 22°C. The resultant mixture was agitated at 22°C until the reaction was monitored by HPLC analysis. Over the reaction period, the pH of the content was monitored and 10% aq. sodium hydroxide was added as required to maintain the pH at 11-12 by pH meter. After the reaction, 10% aq. sodium hydroxide was charged while maintaining the contents at 22°C. The mixture was diluted with DMF and agitated for 2 h. The mixture was filtered over a minimum of 1 h into the first in-process cleaned first reactor, containing water, whilst maintaining the contents at 16°C and then rinsing forward with DMF. The resultant slurry was agitated for 1-3 h at 22°C.

The crude product was filtered and washed with water and then methyl tertiary butyl ether (MTBE). The wet crude product was discharged from the filter and transferred into the first reactor; and ethyl acetate (EtOAc) was charged. The mixture was heated to reflux and agitated at reflux temperature until all the solids are dissolved. The water level must be less than 6.0%. With ramp cooling, the content was adjusted to 22°C over a minimum of 4 h.

The crystallized product was filtered and washed with EtOAc and then charged back to the first reactor. Ethyl acetate (EtOAc) was added. The mixture was heated to reflux and agitated at the temperature until all the solids are dissolved. The water level must be not less than 1.0%. The mixture was filtered,

hot, through a polishing filter into the second reactor (EtOAC preconditioned), rinsed forward with EtOAc.

The product was concentrated under atmospheric pressure. After adjusting to 65°C and charging in EtOAc, the pot was adjusted to reflux and agitated at reflux for ca. 30 minutes. Water content was checked and if the water level was more than 0.2%, the same cycle was repeated.

Once the water level was at maximum 0.2%, the content was adjusted to reflux and then agitated under reflux for 1-3 h. With ramp cooling, the content was adjusted to 22°C over minimum 4 h and then agitated at the temperature for minimum of 8 h.

The product was filtered, washed with EtOAc and dried under vacuum at maximum of 60°C. The product was then milled.

Materials	**M.W.**	**w/w Ratio**	**Mole Ratio**	**v/w Ratio**
3-(2,4-Bis(trifluoromethyl)-phenyl)-6-methylpyridazine,	306.21	1.00	1.00	—
t-Butyl methyl ether	88.15	—	—	—
Diatomaceous Earth (Celite)			—	—
N,N-Dimethylformamide	73.10	6.90	—	7.30
Drinking water	18.02	27.72	—	27.72
Ethyl acetate	88.11	33.90	—	37.70
2-(2-Fluorophenyl)-imidazo-[4,5-c]pyridine, GS-9133	213.21	0.560	0.78	—
Methylene chloride	84.93	16.50	—	12.50
Sodium hydroxide	40.00	0.276	—	—
Trichloroisocyanuric acid	232.41	0.315	0.415	—

5

Nuclear Magnetic Resonance (^{1}H-, ^{13}C-, and ^{19}F-NMR) Spectra

Nuclear magnetic resonance (NMR) spectra of compound (1) is consistent with the proposed structure. The ^{13}C, ^{19}F, and ^{1}H-NMR spectra of compound (1) in DMSO-d_6 were measured using a Varian UnityInova-400 FT-
10 NMR spectrometer. Spectra are shown in the table below. The NMR chemical shift assignments were established using 2D correlation experiments (COSY, HSQC, HMBC and HSQCTOCSY).

5 ^{1}H- and ^{13}C-NMR chemical shift assignments for Compound (1) reference standard

Atom	δC/ppm (DMSO-d_6)	δF/ppm (DMSO-d_6)	δH/ppm (DMSO-d_6)
1A	140.16		
2A	128.32 (q[a], J_{CF} = 32 Hz)		
3A	123.61, m		8.24 (m, 1 H)
4A	130.27 (q, J_{CF} = 34 Hz)		
5A	129.54 (q, J_{CF} = 3 Hz)		8.22 (m, 1 H)
6A	133.36		7.88 (m, 1 H)
7A	123.20 (q, J_{CF} = 273 Hz)	–56.4[b]	
8A	123.02 (q, J_{CF} = 275 Hz)	–62.0[b]	
1	158.76		
2B	128.16		8.01 (d, 1 H, J = 8.4 Hz)
3B	126.20		7.95 (d, 1 H, J = 8.8 Hz)
4B	157.70		
5B	60.49		6.17 (s, 2 H)
2C	131.86		8.31 (m, 1 H)
3C	112.63		7.86 (m, 1 H)
4C	155.44		
6C	168.11 (d, J_{CF} = 6 Hz)		
8C	145.08		
9C	133.06		9.25 (s, 1 H)
1D	123.11 (d, J_{CF} = 10 Hz)		
2D	160.46 (d, J_{CF} = 254 Hz)	–111.7	
3D	116.59 (d, J_{CF} = 22 Hz)		7.29 (m, 1 H)
4D	130.84 (d, J_{CF} = 8 Hz)		7.46 (m, 1 H)
5D	124.13 (d, J_{CF} = 4 Hz)		7.31 (m, 1 H)
6D	131.72 (d, J_{CF} = 2 Hz)		8.35 (m, 1 H)

a. multiplicity, s: singlet, d: doublet, q: quartet, m: multiplet
b. interchangeable signals

Differential Scanning Calorimetry

Compound (1) samples (amorphous) designated "Research lot 6" were made according to the method published as Example 1a in WO 08/005519, which is hereby incorporated by reference in its entirety. The remaining samples were crystalline compound (1). The samples were subjected to measurement using a Differential Scanning Calorimetry (DSC) apparatus (DSC2010, manufactured by TA Instruments Corporation), under nitrogen atmosphere, sample weight 5 ±1 mg, temperature rise rate: either 1°C per min, 5°C per min or 10°C per min, open aluminum pan, and indium standard as a reference. The enthalpy, extrapolated onset temperature and apex temperature at an endothermic peak on the obtained DSC curve were determined.

The DSC results for Research lot 6 and representative crystalline free base compound (1) batches are summarized in Table 1 and Figures 4 and 5, respectively. When the crystal form of compound (1) was subjected to DSC scan at 1°C/min, the enthalpy of the endothermic peak is about 80 J/g, and the extrapolated onset temperature is 233.2°C ±2.0°C. The apex of the endothermic peak is 233.9°C ±3.0°C.

Table 1. Example DSC values obtained for Compound (1) batches

	10 °C/min scan		1 °C/min scan		
	peak onset	main peak	peak onset	main peak	Enthalpy (J/g)
9190 Ref Std	235.8	237.2	233.7	234.6	89.5
9190-A-1	n/a	n/a	234.8	234.0	--
9190-B-1 Crop 1	235.2	237.4	231.6	232.2	78.5
9190-B-1 Crop 2	236.1	238.5	234.3	235.6	80.9
**Research Lot 6	220.2	221.3	pending	pending	39.1

Note: All °C excecpt for enthalpy
**5 °C/min scan reported for Lot 6

X-Ray Powder Diffractometry – Study 1

Samples made by example 1a of WO 05/063744 and by the method of this invention were analyzed in the as received condition, only mixing with a spatula prior to analysis. A sample was fixed to an aluminum cell, and the measurement was performed using an X-ray powder diffractometer (XRD-6000, Shimadzu Lab X, manufactured by Shimadzu Corporation, X-ray source: Cu—Kα1 ray, tube voltage: 35 kV, tube electric current: 40 mA, scan speed: 2º per min, continuous scan mode, sampling pitch: 0.02º, scan range: 4 – 35º, β axis rotation: 60 rpm).

Non-micronized, ascicular compound (1) crystals obtained by the method of this invention have an X-ray powder diffraction pattern having characteristic diffraction peaks at diffraction angles 2θ (º) of 13.46, 15.59, 16.90, 17.48, 23.05 and 30.15 as measured by X-ray powder diffractometer (Figure 1). Note that the non-micronized "high melt" 235°C melt ascicular crystal form of compound (1) tested in this example shows some effects due to preferred

orientation and particle size. As a result, Figure 1 should be considered merely exemplary because varying the crystal size and orientation will change the magnitude of the peaks in the plot. Additionally, the diffraction peak value at the above mentioned diffraction angle 2θ (º) may show slight measurement error due to the measurement instrument or measurement conditions and the like. Typically, the measurement error generally is within the range of about ±0.3. The specification for the Shimadzu XRD-6000 is ±0.04. Further, some variation in peak positions can be expected due to product and experimental variation, so they must be considered approximate.

The 220°C "low melt" solid state form of compound (1) comprised by product made according to the example 1a method (or in the method herein prior to the reslurry step) gives an X-ray powder diffraction pattern consistent with amorphous material (Figure 3).

Compound (1) by the method of this invention typically exhibits intrinsic solubility of 0.7 micrograms/ml, a pKa of 5.8, log P of 2.8; and geometric mean (3 lots) pH solubility profile at pH 2 of 458 micrograms/ml and at pH 7.3, 0.7 micrograms/ml. Geometric mean solubility (3 lots) in simulated intestinal fluids (fasted: pH 6.4, 0.75 mM lecithin, 3 mM sodium taurocholate, 270 mOsmol; fed: pH 5.0, 3.75 mM lecithin, 15 mM sodium taurocholate, 635 mOsmol) were 19.1 micrograms/ml (fasted) and 122 micrograms/ml (fed).

Measured parameters vary from lot to lot, so all of the foregoing parameters except molecular weight should be considered to be approximate.

Titration with acids revealed higher solubility with mesylate (>20 mg/ml) compared to the chloride (about 0.6 mg/mL) or sulfate (about 0.5 mg/mL) counterions.

X-Ray Powder Diffractometry – Study 2

Another sample of crystalline compound (1) prepared by the method of this invention was analyzed in the same fashion as Study 1 except that the X-ray powder diffractometer was a PANalytical X'Pert Pro MPD PW3040 Pro, manufactured by PANalytical Inc., using X-ray source: Cu—Kα ray (1.54059 Å), tube voltage: 45 kV, amperage: 40 mA, scan range: 1 – 55 º2θ, step size: 0.008 º2θ, collection time: 3373 s, scan speed: 0.9º per min, slit: DS: 1/2º, SS: 1/4º, revolution time: 0.5 s, mode: transmission. The results are depicted in Figure 2.

Example 2

Formulation of Compositions Using Compound (1)

Crystalline compound (1) is used as an intermediate to produce pharmaceutically acceptable solutions. The following examples are made on a weight by weight basis to achieve 10% w/w active. To make 12 kg solution, exemplary quantitative compositions of compound (1) capsules, 20 mg and 40 mg are listed below.

Quantitative composition of Compound (1) capsules, 20 mg and 40 mg

Components	% w/w	Capsule Unit Formula (mg/unit)		Compendial Reference	Function
		20 mg	40 mg		
Compound 1	10.00	20.0	40.0	None	Active ingredient
Oleic Acid	84.55	169.1	338.2	NF	Solvent
Polysorbate 80	5.00	10.0	20.0	NF	Surfactant
Butylated Hydroxytoluene (BHT)	0.10	0.2	0.4	NF	Antioxidant
Butylated Hydroxyanisole (BHA)	0.35	0.7	1.4	NF	Antioxidant
Capsule Sealing Solution[a] Ethanol Purified water	---[b] ---[b]	---[b] ---[b]	---[b] ---[b]	USP USP	Capsule sealant --- ---
Capsule Shell, Size 0 Licaps™ White Opaque	N/A	1 each	1 each	None	Capsule shell
Total	**100.00**	**200.0**	**400.0**		

[a] Composition is 1:1 w/w ethanol:water solution.

[b] Removed during the capsule sealing process.

- Container/vessel: 12kg stainless steel
- Weigh the following in order:
- 0.012 kg butylated hydroxytoluene (0.10%)
- 0.035 kg butylated hydroxyanisole (0.35%)

- 1.2 kg Compound (1) free base (10%).
- 0.6 kg Polysorbate 80 (5%) weighed
- 10.153 kg oleic Acid (equivalent to 84.55 g (84.55%))

Solubilized crystalline compound (1) capsules, 20 mg or 40 mg, are manufactured through a series of unit process steps. Compound (1) drug substance, oleic acid, polysorbate 80, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA) are mixed until a solution is achieved. The solution is filled into 2-piece hard gelatin capsules. Closed capsules are subsequently sealed with a hydroalcoholic solution, which is evaporated during the sealing process. A vacuum leak test is performed on sealed capsules prior to packaging.

Alternative Formulations

The crystalline compound of formula (1) optionally is used as an intermediate to be formulated into a solubilized form with the following agents:

- Fatty acids (short, medium, and long chained as well as saturated and unsaturated), typically C4 to C22. Typical fatty acids are linoleic acid, lauric acid, capric acid or oleic acid.
- Alcohols such as ethanol, benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400.
- Surfactants, including both ionic and non-ionic surfactants. Examples of non-ionic surfactants are fatty acid esters of polyoxyethylene sorbitan, sorbitan fatty acid ester, polyoxyethylene castor oil derivatives, polyoxyethleneglycerol oxystearate, polyethyleneglycol 60, hydrogenated castor oil, and/or block copolymers of ethylene oxide and propylene oxide.

- Antioxidants, for example butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbyl palmitate, vitamin E, and/or vitamin E PEG 1000 succinate for chemical stability.
- Viscosity inducer (silicon dioxide, polyethylene glycols, titanium oxide and the like).
- And mixtures of the above

Encapsulation can be performed in a soft elastic gelatin or a hard gelatin or a hard hydroxypropyl methyl cellulose capsule. The liquid formulation (solution or encapsulated solution) provides improved oral bioavailability.

Capsule Filling

The composition and preparation of the soft elastic gelatin capsule is well known in the art. The composition typically comprises from 30-50% by weight gelatin, 10-40% plasticizer or a blend of plasticizers and about 25-40% by weight water. Plasticizers can be glycerin, sorbitol or sorbitol derivatives, propylene glycol and the like or a combination thereof.

Various methods can be used for manufacturing and filling the soft elastic gelatin capsules such as rotary, liner or accogel machine and the like. Hard gelatin or HPMC capsules can be purchased from Capsugel, Greenwood, S.C. and other suppliers. Capsules are filled manually or by capsule filling machine.

Formulation Preparation

In general, the compositions of this invention can be prepared in the following manner. The ingredients are mixed in an appropriate vessel size using an overhead mixer (The mixing tank may be purged with nitrogen). The

pharmaceutically acceptable fatty acid and the pharmaceutically acceptable antioxidant are mixed at room temperature. (The solution may be warmed to appropriate temperature if needed, for example to about 45°C in the case of lauric acid, in order to liquefy the fatty acid). The compound of formula (1) is added and stirred until dissolved. The pharmaceutically acceptable surfactant is added with mixing. The appropriate weight of the resulting mixture is filled into hard gelatin capsules

Additional Formulation Compositions

Formula (1) compound	8.0
PEG 400	82.8
EtOH	9.2
Total	100.0

Formula (1) compound	8.0
EtOH	11.0
PG	7.4
Maisine 35-1	36.8
Cremophor RH40	36.8
Total	100.0

Formula (1) compound	8.0
Oleic Acid	92.0
Total	100.0

Formula (1) compound	8.0
Oleic Acid	73.6
EtOH	9.2
Tween 20	9.2
Total	100.0

Formula (1) compound	8.00%
Oleic Acid	87.40%
Tween 80	4.60%
Total	100.00%

FORMULA (1) COMPOUND	20.00%
Oleic Acid	80.0%
Total	100.0%

FORMULA (1)	
COMPOUND	20.00%
Oleic Acid	76.00%
Tween 80	4.00%
Total	100.00%

FORMULA (1)	
COMPOUND	8.00
Oleic Acid	86.47%
Tween 80	4.60%
Aerosil 200	0.92%
BHT	0.01%
Total	100.0%

FORMULA (1)	
COMPOUND	8.00
Oleic Acid	85.55%
Tween 80	4.60%
Aerosil 200	1.84%
BHT	0.01%
Total	100.0%

FORMULA (1)	
COMPOUND	8.00
Oleic Acid	85.55%
Tween 80	4.60%
Aerosil 200	1.84%
BHT	0.01%
Total	100.0%

FORMULA (1)	
COMPOUND	10.00
Oleic Acid	84.55%
Tween 80	5.00%
BHA	0.35%
BHT	0.1%
Total	100.0%

5

Example 2a

Micronized Formulation of Compound (1)

10 Micronized drug substance (Jet mill-00 at 60-80 psi; 3-4 microns average size, about 7-8 sq. meters/g) was dry blended with lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, tartaric acid, and hydroxypropyl cellulose. The blend was granulated by spraying the blend solution. The granules were dried in a fluid-bed. The dried granules were
15 sized by passing through a mill, and then blended with additional microcrystalline cellulose and croscarmellose sodium. The powder blend was lubricated by adding magnesium stearate and then compressed into tablets using a rotary tablet press. The tablets were subsequently film-coated.

20 The table below is a summary of various formulations tested in dogs dosed at 40 mg compound (1), corresponding to approximately 4 mg/kg. The table illustrates the superior performance of the solubilized compound (1) formulations.

In-vivo Data Summary

Dosage Form	Process	Formula	Drug Load (%)	Cmax (μM)	AUC_{24} (μM hr)	F (%)	RSD (%)
Solid	Powder Fill[a]	PIC	50	0.7	2.9	8	52
Solubilized	Liquid Fill	Capric acid	20	4.8	25	79	17
		Lauric acid	20	2.6	14.3	44	29
		Oleic Acid	8	3.8	23	67	27
			20	2.1	14	44	56
			25	7.9	42	125	24
Solid	High Shear[a]	SLS only	20	0.4	4.4	13	85
		SLS & Tartaric	20	0.4	2.7	8	82
		SLS & Tartaric[b]	20	0.9	6.9	20	67
	Fluid bed[a]	SLS & Tartaric	20	0.3	4.4	14	77

[a] Utilizes micronized API

[b] Dosed in dogs treated with pentagastrin to reduce stomach pH

Example 3

Antiviral Activity of Compound (1)

The compound of this invention exhibits anti-HCV replicon activity (assay described in WO 05/063744) against both genotypes 1a and 1, extremely low cytotoxicity (>50,000 nM in Huh-7, HepG2 and MT4 cells), and a highly favorable selectivity index. The compound is substantially less active against genotype 2a.

Activity of Compound 1 Against HCV Genotype 1 and 1a Replicons

HCV genotype 1 (Con-1/lucneo) and 1a (H77/neo) replicon cells were incubated with serial dilutions of compound (1) 2'C-methyl adenosine (2'CMeA) or IFNα for 3 days in the absence or presence of 40 mg/mL human serum albumin (HSA). After incubation, replicon RNA levels in the treated

cells were determined by either a luciferase reporter assay (1 replicon) or a quantitative real-time PCR assay (1a replicon) and the data points were used to calculate EC_{50} (50% effective inhibiting concentration) values for the inhibitors. Compound (1) was shown to inhibit both genotype 1 and genotype 1a replicons with EC_{50} values of 0.6 and 3.6 nM, respectively (Table A). In the presence of human serum albumin, the EC_{50} value of Compound (1) was increased to 11 nM.

Table A: Activity of Compound (1) against HCV Genotypes 1a and 1 Replicons

	EC_{50} [nM][a]		
Compound	HCV 1-lucneo	HCV 1-lucneo 40 mg/mL HSA	HCV-1a
1	0.6 ± 0.28	11	3.6 ± 1.4
2'CMeA	175 ± 70	250	170
IFN-α	2 IU/mL	n.d.	n.d.

n.d., not determined; HSA, human serum albumin

a Mean EC_{50} value and standard error determined from at least 4 independent experiments

Activity of Compound (1) Against HCV Genotype 1a Replicon and Virus

The antiviral activity of compound (1) against HCV genotype 2a was tested in cells chronically infected with the genotype 2a virus as well as in cells replicating a subgenomic 2a replicon. Huh-7 cells containing chronically replicating HCV genotype 2a (J6/JFH-Rluc) virus or subgenomic replicons were cultured with compound (1) or 2'CMeA for 3 days in the absence of human serum albumin. After cultivation, the amount of luciferase in 2a-virus containing cells and HCV NS3 protease activity in the 2a replicon-containing

cells was determined using Promega's luciferase assay and a novel time-resolved fluorescence assay, respectively.

The antiviral activity of compound (1) was significantly reduced in both the HCV-2a chronically infected cell culture model (EC_{50} = 2.9 μM) and the 2a subgenomic replicon model (EC_{50} = 21.9 μM) compared to Huh-7 cells replicating an HCV-1 subgenomic replicon (EC_{50} = 0.0006 μM) (Table 2). Taken together, these results suggest that the reduction in potency for compound (1) against HCV genotype 2a may be due to the genotypic differences between genotype 1 and genotype 2 of HCV.

Table B: Activity of Compound (1) against HCV Genotypes 1 and 2a

	EC_{50} [nM][a]		
Compound	HCV 1-lucneo (subgenomic replicon)	HCV 2a (subgenomic replicon)	HCV-2a (reporter virus)
1	0.6 ± 0.28	21898 ± 18972	2900 ± 1250
2'CMeA	175 ± 70	1610 ± 1099	194 ± 26
IFN-α	2 IU/mL	n.d.	1.2 IU/mL

n.d., not determined; HSA, human serum albumin

a Mean EC_{50} value and standard error determined from at least 4 independent experiments

Compound (1) was evaluated for its cytotoxicity in a variety of cell types including HCV replicon-containing cell lines (Huh-7, SL3 and MH4) and non-replicon-containing cell lines (HepG2, MT4), using a CellTiter-Glo Luminescence Cell Viability assay (Promega). No toxic effects were observed in any of the cell lines at the highest concentration tested (50 μM) (Table C). These results, coupled with its potent antiviral activity (EC_{50} = 0.62-3.6 nM) in HCV-1

and HCV-1a replicons, indicates a high selectivity index (CC_{50}/ EC_{50}>13,000-80,000) for compound (1).

Table C: Cytotoxicity of compound (1) in HCV Replicon Containing Cell Lines

	CC_{50} [μM][a]				
Compound	Huh-7 lucneo[b]	SL3[b]	MH4[b]	HepG2	MT4
1	> 50	> 50	> 50	> 50	> 50
2'CMeA	7.2 ± 6	3.9	16	24.3 ± 2.1	3.5 ± 1.9

n.d., not determined; HSA, human serum albumin

a Mean CC_{50} value and standard error determined from at least 4 independent experiments
b HCV replicon-containing cell lines

Anti-HCV Activity of Compound (1) in Combination with IFN In Vitro

Pegylated interteron-α (PEG-IFN-α), in combination with ribavirin, represents the current standard of care for HCV-infected patients. *In vitro* combination studies of compound (1) and IFN-α were performed in replicon cells. Data was analyzed using the MacSynergy template developed by Prichard and Shipman. Results from these studies suggest an additive interaction between compound (1) and IFN-α.

Example 4

Antiviral, Pharmacokinetic and Safety Data for Compound (1) in a Phase-1, First-In-Human Trial in HCV Genotype 1-Infected Subjects.

A randomized, double-blind, placebo controlled trial was designed to evaluate the safety/tolerability, phamacokinetics and antiviral activity of single (in Part A) and multiple (in Part B) doses of Compound (1) (oleic acid solution,

above) in subjects chronically infected with HCV genotype 1 (GT-1) without decompensated cirrhosis. Prospective subjects are 18-60 years of age, are HCV treatment naïve, and are in general good health.

In completed Part A, five successive cohorts of 6 subjects were randomized (5:1) to receive single ascending doses of Compound 1 (40, 120, 240, 240-with food, or 480 mg) or placebo. In ongoing Part B, four successive cohorts of 12 subjects are randomized (10:2) to receive multiple ascending doses of Compound 1 (40 mg BID, 120 mg BID, 240 mg QD, 240 mg BID) or placebo, over 8 days.

Thirty-one subjects enrolled in Part A were of mean age 43.6 years, predominantly male (20/31), Caucasian (25/31), and infected with either HCV Genotype-1a (24) or 1 (6). Median (range) baseline HCV viral load was 6.6 Log^{10} RNA IU/mL (5.2-7.3). Single doses of compound (1) were well tolerated, with no serious or treatment-limiting adverse events (AEs) reported. The most common AE was headache. All AEs were mild in severity, with the exception of one moderate headache. There were no Grade 3 or 4 treatment emergent laboratory abnormalities.

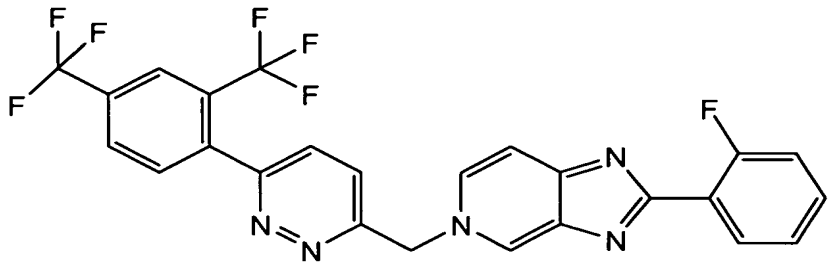
Median compound (1) plasma half-life ranged from 10 to 15 hours across cohorts. Systemic exposure was increased approximately 2-fold when compound (1) was administered with a high fat meal. Mean compound (1) concentration 24 hours after the 240 mg fasted dose dosing was ~7-fold higher than the protein binding adjusted *in vitro* HCV GT-1 Replicon EC_{50} value. Following single-dose exposure, maximal antiviral effect was observed at 24 hours, with median declines ranging from 0.46 to 1.49 Log^{10} HCV RNA IU/mL

across cohorts. Individual HCV RNA declines among all compound (1) recipients ranged from 0.19 to 2.54 $\log^{10}$ IU/mL following single-dose exposure.

This is the first clinical demonstration of antiviral activity of compound (1). Single dose exposure to compound (1) was well tolerated, demonstrated favorable PK properties and potent antiviral activity.

We claim:

1. A crystalline compound of formula (1)



(1)

and its salts, which is substantially free of amorphous compound (1) .

2. The crystalline compound of claim 1 having an endothermic onset at about 235°C in differential scanning calorimetry (DSC) profile.

3. The crystalline compound of claim 2 having a heat of fusion (DH_f) of about 81 J/g (42 KJ/mole).

4. The crystalline compound of claim 3 having at least one approximate peak at diffraction angle 2θ (º) of about 17 as measured by X-ray powder diffractometry.

5. The crystalline compound of claim 1 which is the free base.

6. The crystalline compound of claim 1 in the form of needles or rods.

7. A composition comprising the crystalline compound of claim 1 containing less than about 40% by weight of the amorphous compound (1).

8. A composition comprising the crystalline compound of claim 7 which contains less than about 10% by weight of amorphous compound (1).

9. A composition comprising the crystalline compound of claim 8 wherein the crystalline compound (1) contains less than about 100 ppm chloride.

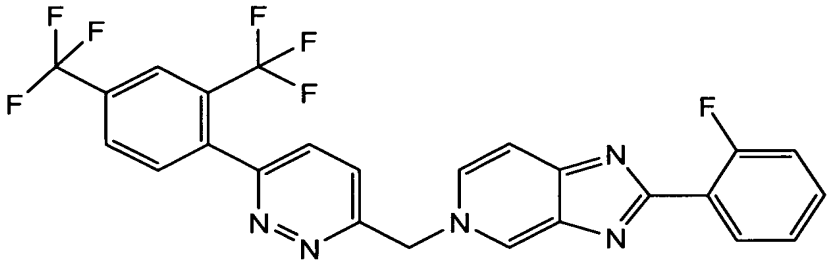
10. The crystalline compound of claim 1 which has been micronized.

11. The crystalline compound which is the free base substantially free of amorphous compound (1) and any other crystal form of compound (1).

12. The crystalline compound of claim 1 which is substantially free of the chloride salt of compound (1).

13. A composition comprising the crystalline compound of claim 1 and a pharmaceutically acceptable excipient.

14. A method for making crystalline compound (1)



comprising crystallizing compound (1) from crystallization solvent and controlling the amount of water in the crystallization solvent.

15. The method of claim 14 wherein the compound (1) is crystallized from ethyl acetate or ethyl acetate/isopropyl alcohol solvent containing less than about 0.9% by weight of water in the solvent.

16. The method of claim 14 wherein the amount of water is controlled such that less than about 10% by weight of amorphous compound (1) is precipitated during crystallization.

17. The method of claim 14 wherein the water is controlled by removing it azeotropically from the crystallization solvent.

18. The method of claim 14 comprising providing water in the crystallization solvent at a concentration of less than about 10%.

19. The method of claim 18 comprising a plurality of crystallization steps, wherein crystallization is effected from solvents comprising successively lower concentrations of water.

20. The method of claim 18 wherein the last crystallization step is effected from solvent comprising less than about 0.9% water.

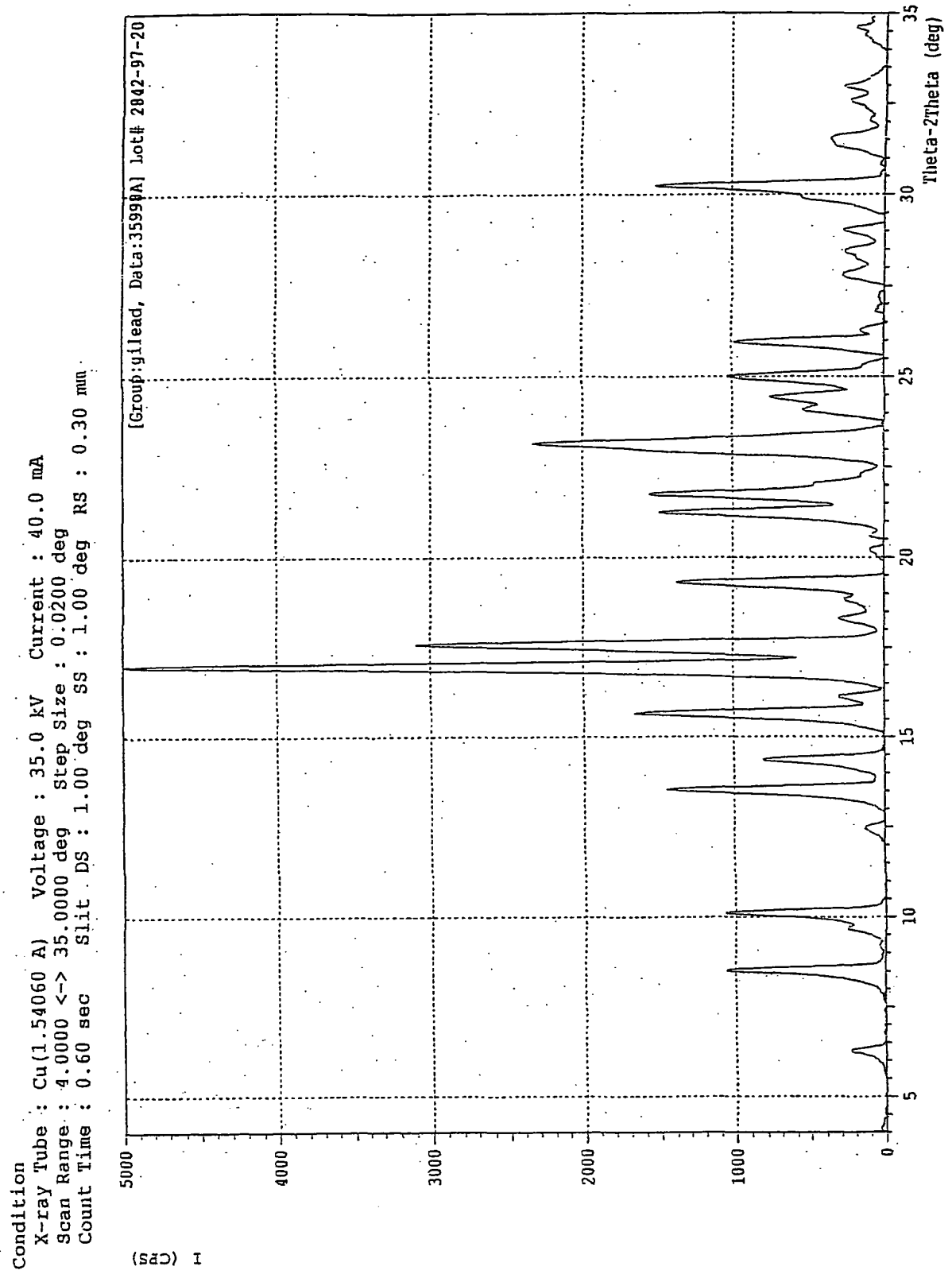

[Group:gilead, Data:35990A] Lot# 2842-97-20
Condition
X-ray Tube : Cu(1.54060 A) Voltage : 35.0 kV Current : 40.0 mA
Scan Range : 4.0000 <-> 35.0000 deg Step Size : 0.0200 deg
Count Time : 0.60 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm
I (CPS)
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
35
Theta-2Theta (deg)

Figure 1/5

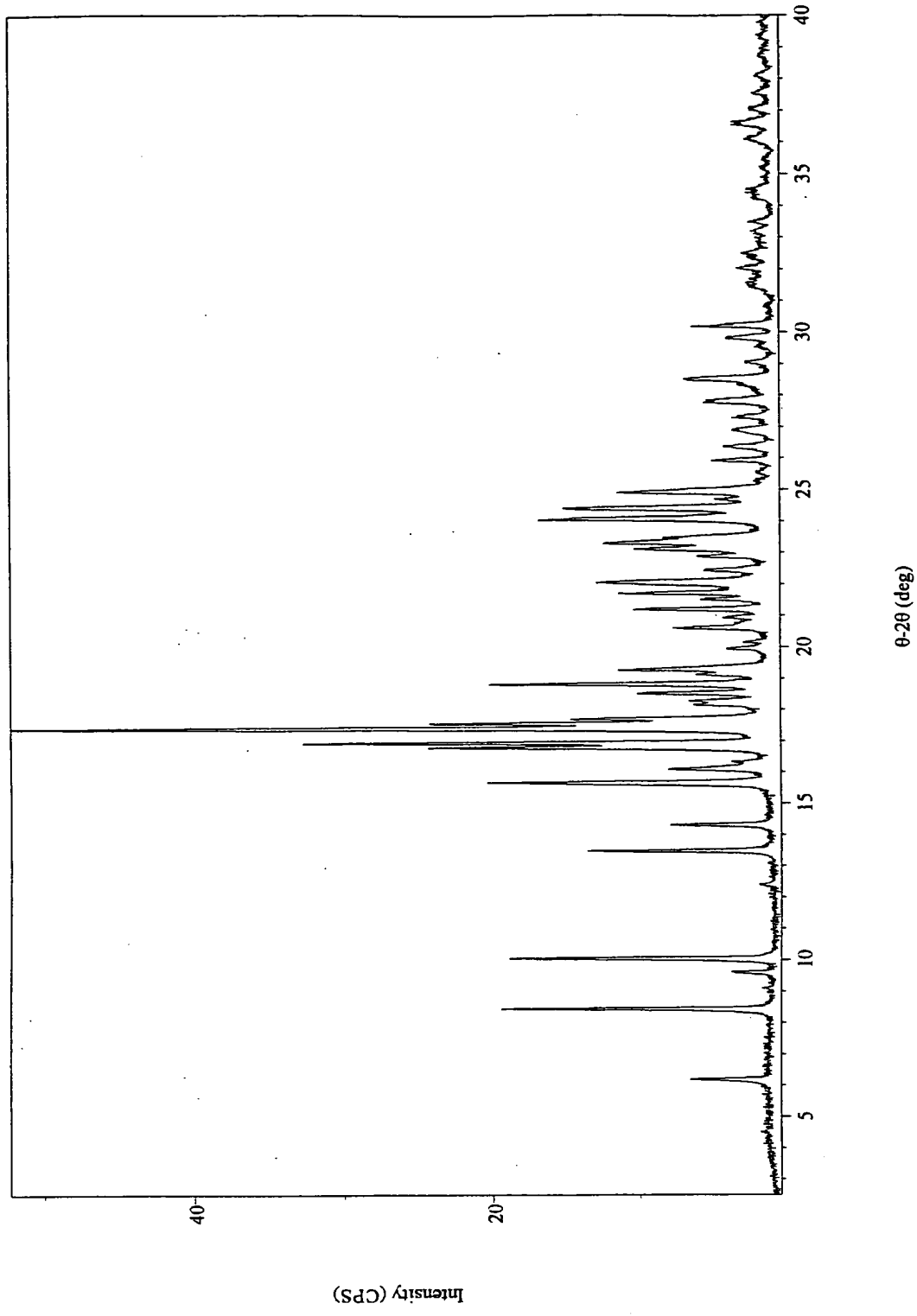
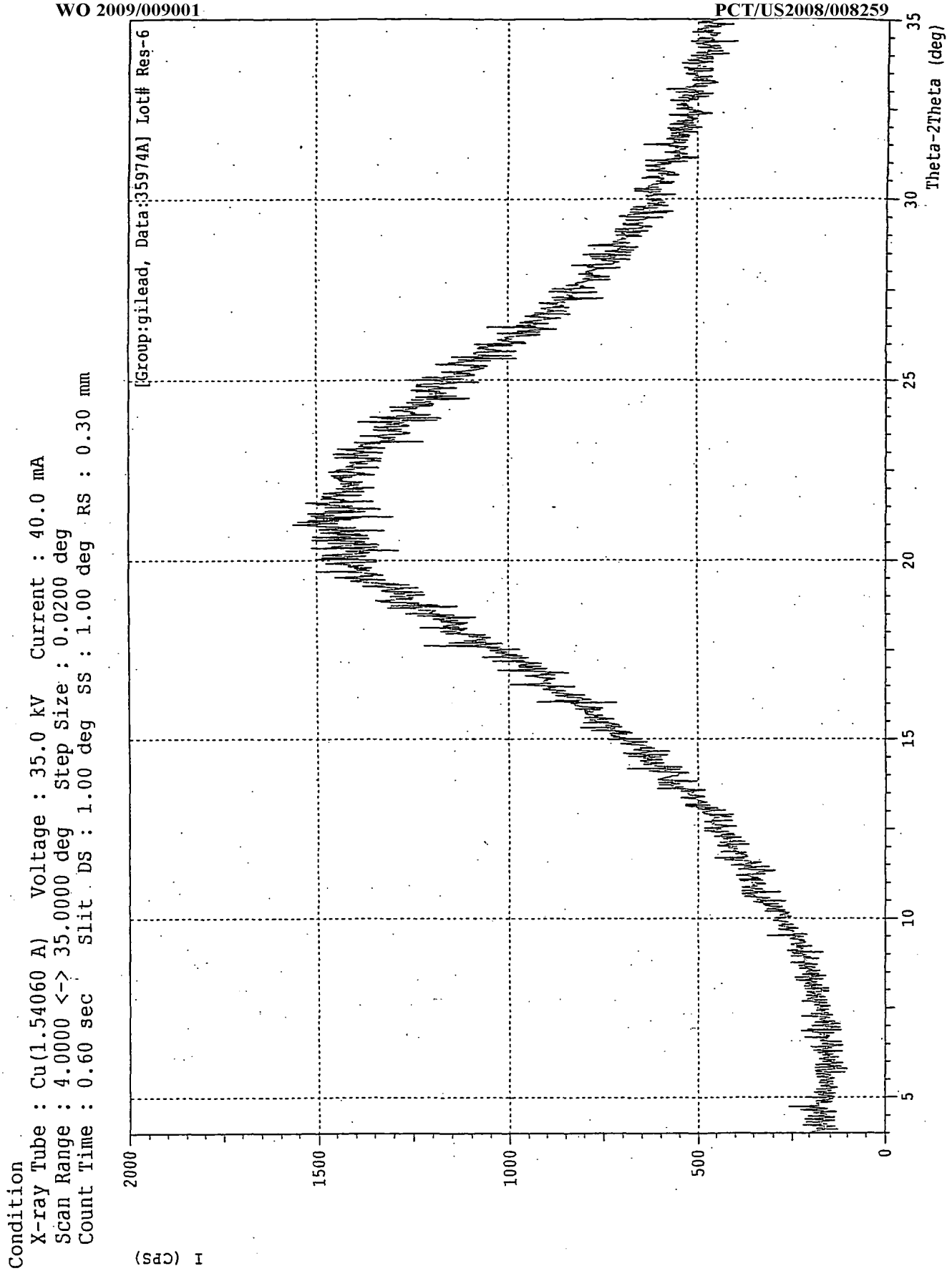


Figure 2/5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Condition
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Count Time : 0.60 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm
I (CPS)
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1500
1000
500
0
5
10
15
20
25
30
35
Theta-2Theta (deg)

Figure 3/5

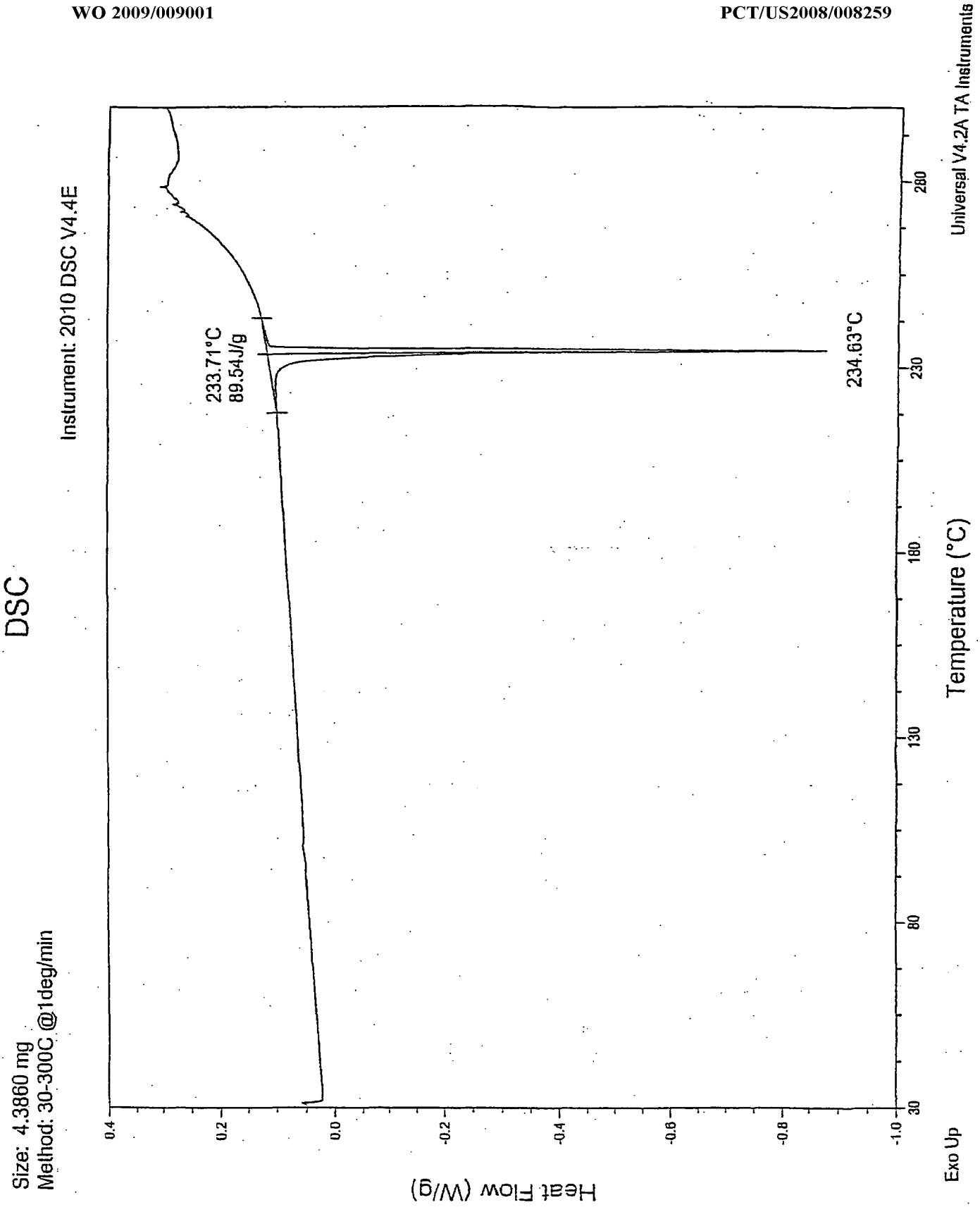
DSC
Instrument: 2010 DSC V4.4E
Size: 4.3860 mg
Method: 30-300C @1deg/min
233.71°C
89.54J/g
234.63°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V4.2A TA Instruments

Figure 4/5

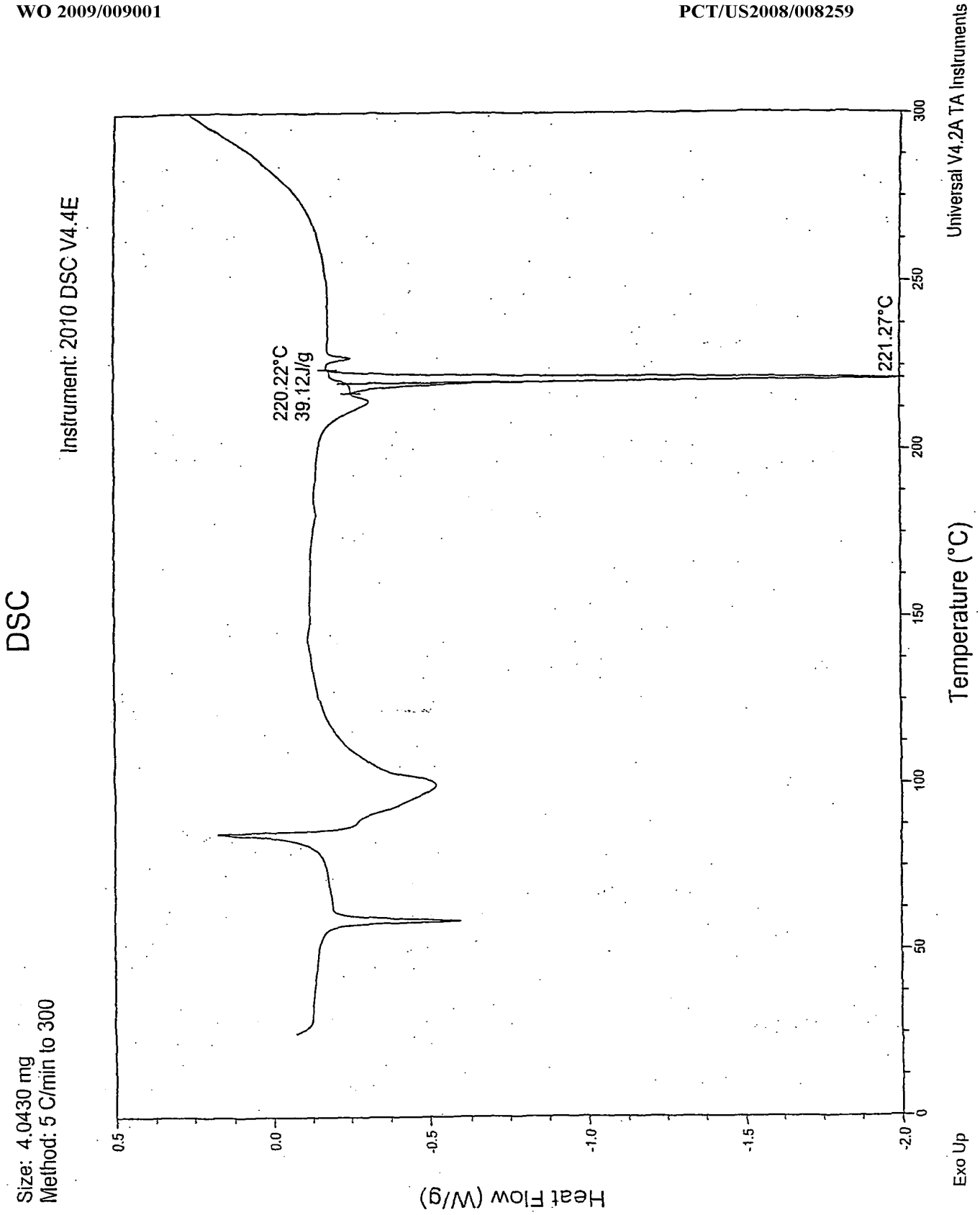
DSC
Instrument: 2010 DSC V4.4E
Size: 4.0430 mg
Method: 5 C/min to 300
220.22°C
39.12J/g
221.27°C
Heat Flow (W/g)
Temperature (°C)
Exo Up
Universal V4.2A TA Instruments
0.5
0.0
-0.5
-1.0
-1.5
-2.0
0
50
100
150
200
250
300

Figure 5/5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/008259

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4353 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/063744 A (LEUVEN K U RES & DEV [BE]; PUERSTINGER GERHARD [AT]; GILEAD SCIENCES I) 14 July 2005 (2005-07-14) cited in the application example 317	1-20
P,X	WO 2008/005519 A (GILEAD SCIENCES INC [US]; LEUVEN K U RES & DEV [BE]; PUERSTINGER GERHA) 10 January 2008 (2008-01-10) cited in the application example 1b	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2008	14/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Usuelli, Ambrogio

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/008259

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005063744 A	14-07-2005	AU 2004309390 A1	14-07-2005
		CA 2549606 A1	14-07-2005
		EP 1706403 A2	04-10-2006
		JP 2007518720 T	12-07-2007
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(74) Agents: **WONG, James, J.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

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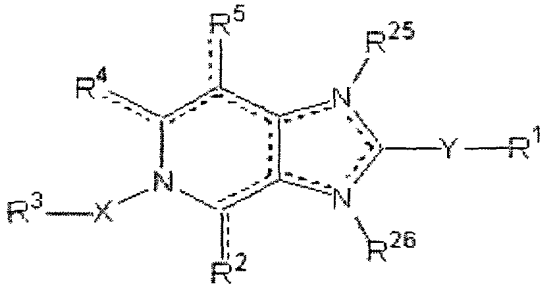
(54) Title: IMIDAZO[4,5-c]PYRIDINE COMPOUNDS AND METHODS OF ANTIVIRAL TREATMENT



(A)

(57) Abstract: The present invention relates to pharmaceutical compositions for the treatment or prevention of viral infections comprising as an active principle at least one imidazo[4,5-c]pyridine prodrug having the general Formula (A) wherein the substituents are described in the specification. The invention also relates to processes for the preparation and screening of compounds according to the invention having above mentioned general Formula and their use in the treatment or prophylaxis of viral infections.

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Deutsch, W

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10 August 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZO[4,5-C]PYRIDINE COMPOUND AND METHOD OF ANTIVIRAL TREATMENT

(57) Abstract: The compound 5-((3-(2, 4-trifluoromethyphenyl)isoxazol-5-yl)methyl)-2-(25 fluorophenyl)-5H-imidazo[4,5-c]pyridine, together with the salts and solvates thereof. Also provided are compositions comprising this compound and pharmaceutically acceptable carriers, as well as the use of such compositions in the treatment or prophylaxis of viral infections.

WO 2006/069193 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/046477

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15) the whole document	1-5
P,X	WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005 (2005-07-14) abstract; example 6	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another *citation or other special reason* (as *specified*)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" *later document published after the international filing date* or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 2006	13/06/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stroeter, T

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/046477

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3 and 4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/046477

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004005286 A	15-01-2004	AU 2003243846 A1	23-01-2004
		BR 0312547 A	26-04-2005
		CA 2491243 A1	15-01-2004
		CN 1678612 A	05-10-2005
		EP 1521754 A2	13-04-2005
		JP 2005537248 T	08-12-2005
		MX PA04012965 A	16-05-2005
		US 2005239821 A1	27-10-2005
WO 2005063744 A	14-07-2005	NONE	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/026606

A. CLASSIFICATION OF SUBJECT MATTER
C07D473/00 C07D471/04 C07D519/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15) examples, pages 46-52 and 87-89; page 4, lines 5-18 and pages 119-126 page 87 - page 89; examples	56-59,61
X	EP 1 132 381 A (CERMOL S.A) 12 September 2001 (2001-09-12) example 51	56-58,61
A	EP 1 162 196 A (JAPAN TOBACCO INC) 12 December 2001 (2001-12-12) abstract; claims	1-78

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2006	01/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Frelon, D

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/026606

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/20400 A (AXYS PHARMACEUTICALS, INC; HATAYE, JASON, M; RICE, KENNETH; SHELTON, E) 13 April 2000 (2000-04-13) page 1; claims	1-78
A	WO 95/02597 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 26 January 1995 (1995-01-26) abstract; claims	1-78
A	GB 2 158 440 A (FARMITALIA CARLO * ERBA S P A) 13 November 1985 (1985-11-13) abstract; claims	1-78
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YUTILOV, YU. M. ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" XP002367158 retrieved from STN Database accession no. 1989:165603 abstract & KHIMIKO-FARMATSEVTICHESKII ZHURNAL, vol. 23, no. 1, 1989, pages 56-59,	1-78
A	WO 01/95910 A (BRISTOL-MYERS SQUIBB COMPANY) 20 December 2001 (2001-12-20) abstract; claims	1-78
A	EP 1 386 923 A (SUMITOMO PHARMACEUTICALS COMPANY, LIMITED) 4 February 2004 (2004-02-04) abstract; claims	1-78
A,P	WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005 (2005-07-14) the whole document	1-78

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/026606

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 71-74 and 75-78 are directed to a method of treatment of the human/animal body and/or to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/026606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004005286 A	15-01-2004	AU 2003243846 A1	23-01-2004
		BR 0312547 A	26-04-2005
		CA 2491243 A1	15-01-2004
		CN 1678612 A	05-10-2005
		EP 1521754 A2	13-04-2005
		JP 2005537248 T	08-12-2005
		US 2005239821 A1	27-10-2005
EP 1132381 A	12-09-2001	AU 3591301 A	17-09-2001
		WO 0166526 A1	13-09-2001
EP 1162196 A	12-12-2001	AU 763356 B2	17-07-2003
		AU 2401701 A	09-07-2001
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		CZ 20013424 A3	13-02-2002
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		ID 30204 A	15-11-2001
		WO 0147883 A1	05-07-2001
		NO 20014134 A	22-10-2001
		NZ 514403 A	25-10-2002
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		TR 200103147 T1	21-06-2002
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WO 9502597 A	26-01-1995	AT 195735 T	15-09-2000
		AU 693747 B2	02-07-1998
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		AU 681687 B2	04-09-1997
		AU 7247594 A	13-02-1995
		CA 2167042 A1	26-01-1995
		CZ 9600105 A3	12-06-1996
		DE 69425661 D1	28-09-2000
		DE 69425661 T2	19-04-2001
		DK 708772 T3	18-09-2000
		EP 0708772 A1	01-05-1996
		ES 2149276 T3	01-11-2000
		IL 110091 A	18-03-1997
		JP 9500128 T	07-01-1997
		MX 9405383 A1	31-01-1995
		US 5366974 A	22-11-1994
		US 5446153 A	29-08-1995
		US 5494916 A	27-02-1996
GB 2158440 A	13-11-1985	BE 902611 A1	30-09-1985
		DE 3521303 A1	31-10-1985
		JP 61167687 A	29-07-1986
WO 0195910 A	20-12-2001	AU 7290601 A	24-12-2001
		BR 0111569 A	29-04-2003
		CA 2412327 A1	20-12-2001
		CN 1436079 A	13-08-2003
		CZ 20024078 A3	13-08-2003
		EP 1311268 A1	21-05-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/026606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0195910 A		HU 0400766 A2	28-07-2004
		JP 2004503501 T	05-02-2004
		MX PA02012204 A	15-10-2003
		NO 20025977 A	29-01-2003
		NZ 523566 A	27-08-2004
		PL 360290 A1	06-09-2004
EP 1386923 A	04-02-2004	CA 2444130 A1	31-10-2002
		CN 1512992 A	14-07-2004
		WO 02085905 A1	31-10-2002
		US 2004132748 A1	08-07-2004
WO 2005063744 A	14-07-2005	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 111.23F	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043112	International filing date *(day/month/year)* 21.12.2004	Priority date *(day/month/year)* 22.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D471/04 A61K31/437		
Applicant K.U. LEUVEN RESEARCH & DEVELOPMENT		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 20 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.10.2005	25.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deutsch, W Telephone No. +49 89 2399-8281

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043112

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 4-243	as originally filed
3	filed with telefax on 05.12.2005

Claims, Numbers

1-69	filed with telefax on 05.12.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-69
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-69
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III

For the assessment of the present claims 64-69 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 64-69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V and VI

Reference is made to the following documents:

D1: EP-A-1 132 381 (CERMOL S.A) 12 September 2001 (2001-09-12)
D2: US-A-5 302 601 (KHANNAL ET AL) 12 April 1994 (1994-04-12)
D3: US-A-4 990 518 (KHANNA ET AL) 5 February 1991 (1991-02-05)
D4: WO 96/12703 A (G.D. SEARLE & CO; KHANNA, ISH, KUMAR; STEALEY, MICHAEL, ALLAN; WEIER,) 2 May 1996 (1996-05-02)
D5: US-A-5 486 525 (SUMMERS, JR. ET AL) 23 January 1996 (1996-01-23)
D6: EP-A-0 076 530 (JANSSEN PHARMACEUTICA N.V) 13 April 1983 (1983-04-13)
D7: US-A-5 585 492 (CHANDRAKUMAR ET AL) 17 December 1996 (1996-12-17)
D8: US-A-5 137 896 (VAN DAELE ET AL) 11 August 1992 (1992-08-11)
D9: WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004 (2004-01-15)

D10: EP-A-0 417 745 (G.D. SEARLE & CO) 20 March 1991 (1991-03-20)

D11: WO 99/27929 A (MERCK & CO., INC; HALCZENKO, WASYL; STUMP, CRAIG, A) 10 June 1999 (1999-06-10)

D12: US-A-5 227 384 (KHANNA ET AL) 13 July 1993 (1993-07-13)

D13: US-A-5 446 032 (WHITTAKER ET AL) 29 August 1995 (1995-08-29)

D14: EP-A-0 344 414 (G.D. SEARLE & CO) 6 December 1989 (1989-12-06)

D15: US-A-5 011 832 (DININNO ET AL) 30 April 1991 (1991-04-30)

D16: GB-A-2 158 440 (FARMITALIA CARLO ERBA S P A) 13 November 1985 (1985-11-13)

D17: RYUICHI ET AL:: "Synthesis and Evaluation of Novel Nonpeptide Angiotensin II Receptor Antagonists: Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent" CHEM. PHARM. BULL, vol. 43, no. 3, 1995, pages 450-460, XP001206481

D18: THOMAS D. PENNING ET AL.: "Synthesis of Imidazopyridines as Potent Inhibitors of Leukotriene A4 Hydrolase" BIOORGANIC AND MEDICINIAL CHEMISTRY LETTERS, vol. 13, 2003, pages 1137-1139, XP002333169

D19: YUTILOV YU M ET AL: "Synthesis and antiviral activity of spinaceamine derivatives" 1989, CAPLUS , XP002265211

D20: G.B. BERLIN, "Ionisation Constants of Heterocyclic Subsatnces, Part VIII, 1,3,5 Triazindenes, Physical, Journal of the Chemical Society[SEction B]: Physical Organic, vol.4 , 1966, pages 285-291

D21: RYUCHI KIYAMA"Synthesis and Evaluation of Novel NonpeptideAngiotensin II Receptor Antagonists": Imidazo[4,5-c]pyridine Derivatives with an Aromatic Substituent, Chem. Pharm. Bull. 43(3), pages 450-460.

D22: GERHARD CLEVE ET AL., Derivate des Imidazo[4,5-b]- und Imidazo[4,5-c]pyridins., Liebigs Ann. Chem., 747,1971, pages 158-171

D20-D22 were cited in the internationational search report, but are mentioned in the description of the present application.

D9 has a publication date, which is prior to the filing date of the present application. It may be noted that D9 has entered the European phase of examination.

The present claims do not appear to be entitled to the earlier priority date of 22.12.2003, such that D9 is relevant both for the examination of novelty and inventive step.

Novelty

Novelty destroying subject matter

Example 51 of D1 is novelty destroying to the present claim 1.and a number of further claims. (The subject matter of the claims differs from further examples in D1 from through the fact that R^3 does not include saturated heterocycles).

5-[(4-fluorophenyl)methyl]-N-methyl-5H [4,5-c]pyridine-2-amine disclosed on page 75, lines 26-27 of D6 and column 43, lines 38 and 39 of D8 is still novelty destroying to the present claim 1 and a number of further claims.

The subject matter of the present claims overlaps with that of D9. This overlap is considered to be novelty destroying to the present claims.

D9 also contains numerous examples in table 8, which are novelty destroying for the present claims e.g. entry 2,3, 5, 12, ,24, 26 etc. The number of compounds, which are novelty destroying to the present claims which are novelty destroying will depend on the final interpretation of the term "aryl" and "aromatic heterocycle"(see section VIII). Thus e.g.entry 23 of D9 could be novelty destroying for a number of claims.

Differences with subject matter of cited documents

The compounds of the present claims differ from the compounds of D2- D4, D7, D10-D15, D17, D21 through the proviso introduced into claim 1, that $Y\text{-}R^1$ is not hydrogen or alkyl or in the case of claim 56 that $Y\text{-}R^1$ does not include alkyl or hydrogen.

The compounds of the present claims are considered to be a novel selection from those generally disclosed in D5. The compounds of the present claims either differ from those specifically disclosed in D5 through the proviso that $Y\text{-}R^1$ is not alkyl or through the $R^3\text{-}X$ group in claim 56.

The imidazopyridine derivatives of the present claims differ from those of D16 through the number of double bonds. In claim 1 of the present claims it is indicated that the dotted lines represent at least 3, whereas in the compounds of D16, there is only 1 double bond in the tetrahydroimidazopyridine structure.

The compounds of the present claim 1 differ from 1,4,6,7-tetrahydro-1-methyl-2-(methylthio)-alpha-phenyl-5H-imidazo[4,5-c]pyridine-5-ethanol disclosed in D19 through the the number of double bonds in the bicyclic structure, through the proviso that when when one of R^{25} or R^{26} is present then either R^2 or R^4 is selected from (=O), ((=S) and (=NR^7), and the OH group.

The compounds of the present claim 1 differs from that of 5methyl-2-methylthiotriazaindene disclosed in D20 through the proviso that when when one of R^{25} or R^{26} is present then either R^2 or R^4 is selected from (=O), ((=S) and (=NR^7).

It has been assumed that the term "aryl" in claim 1 does not include substituted aryl. In this case compounds 9a and 9b of D22 (page 747) are not novelty destroying to the present claim 1, 48 and 56 (see however section VIII). However, final interpretation will depend on the course of the examination, at the regional stage.

Inventive Step

The closest prior art is considered to be D9, in view of the novelty destroying subject matter that this contains and in that it relates to compounds having antiviral activity.

In view of the disclosures of D9, the skilled person would readily have arrived at the claimed subject matter.

The problem underlying the invention is considered to be the provision of further imidazopyrimidine compounds having a surprising activity compared to the closest prior art.

In the absence of any evidence for such a surprising effect an inventive step cannot be acknowledged.

Furthermore an inventive step cannot however be acknowledged for the present claims for the following reasons:

Reasonable alternatives to the tested examples are allowable. The claims however include modifications of substituents which would not reasonably be expected to solve the problem underlying the invention having regard for common knowledge and biological structure-activity relationships.

The question as to what extent the structure of a chemical compound can be modified without causing major changes in its biological activity is considered to be equally relevant in respect of the question as to whether or not it is credible that all members of a certain group of chemical compounds solve a particular problem.

In the present case the structural differences on passing from the examples to compounds falling in the claims are far greater than the structural differences between compounds falling under the claims and compounds according to the prior art D16 and D19.

For example In the present case -Y-R^1 is limited to halophenyl compounds, whilst Y-R^1 includes variations, which are structurally completely different to this.

VIII

a)The description has not been amended to the new set of claims, leading to an inconsistency between the claims. The present claims are therefore not supported by the description as required by Article 6 EPC.

In this respect the following is to be noted.

-The description refers to the exclusion of various compounds as required on page 28, last line to page 31, line 3. The different scope of exclusion and the fact that they need not be excluded in the description leads to an inconsistency with the claims,

The Applicant has indicated that these disclosures could be removed from the description in due course, if these are not required as a basis for a proviso to distinguish the claim from the prior art.

-There is an inconsistency between the claims and description with respect to the term "aryl", such that the meaning of the claims is not clear from the wording alone.

Thus according to the claims R^3 may be aryl which may be substituted by M-Q.

"Aryl" would normally be understood according to the IUPAC rules as only containing carbon and hydrogen. Since M-Q cannot be e.g. fluorine or CF_3 and these substituents are found on the phenyl group in e.g. example 19 and 20, there is an implication in the light of the description that aryl is intended to encompass "optionally substituted" aryl.
This appears to be supported from the compounds which it is intended to exclude from the invention (see e.g. page 26, lines 30-34).

Similar arguments apply to "aromatic heterocycle".

b)The reasons for the provisos in the claims are only partially explained by the cited prior art and it will become necessary to consider more closely the reasons for the provisos in the present claims.

For example, the proviso may be directed to the exclusion of known prior art compounds which do possess the desired activities.

If in this case, if the said prior art was published before the priority date of the application, it may be necessary to take the prior art into consideration for the assessment of inventive step.

Similarly the reason for the possible exclusion (a) on page 26 and page 29, lines 23 page 29, line34and page 33, line 35

Furthermore it may be necessary to consider why there are differences in the scope of proviso in claims 1 and 2 with respect to the substituent R^3 and is absent in claim 3.

b) The expressions "an amino acid residue" in the claims is considered to be unclear, since the expression gives no indication which part of the molecule of said compounds is intended as substituent. For example the amino acid residue could be such diverse groups as a COOH group, a CH_3 group a HO-benzyl group or HO-benzyl-CH_2-CH(COOH)-NH-. Furthermore it is unclear whether amino acid residue encompasses only the common natural amino acids or whether it is also intended to cover synthetic amino acids or less common amino acids.

If not all of the diverse possibilities are intended e.g. methyl, it is unclear where the bordelines for the definition lie.

The meaning of the terms of a claims should be as far as possible be clear from the wording alone. The expression "an amino acid residue as used in the claims relies on the description for its interpretation".

c) Having regard for claims 1, 2, 3, 48, 56 it appears that these are independent claims. It is however considered that it would be appropriate to cover these by a single independent claim.

d) a lack of clarity arises with certain R^6 substituents, which are unstable. Thus for example OH substituted by -O-alkenylC(=O)OR^{18}.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 691.P2F	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2007/015553	International filing date *(day/month/year)* 06 July 2007 (06.07.2007)	Priority date *(day/month/year)* 07 July 2006 (07.07.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GILEAD SCIENCES, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 13 January 2009 (13.01.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/015553	06.07.2007	07.07.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/14 A61K31/4353 A61P31/12

Applicant
GILEAD SCIENCES, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	BOURGHIDA, E Telephone No. +31 70 340-9517

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/015553

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 16-21 (with respect to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 16-21 (with respect to industrial applicability) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15,22-27
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 Claims 16-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2.1 Reference is made to the following documents:

D1: WO 2005/063744 A (LEUVEN K U RES & DEV [BE]; PUERSTINGER GERHARD [AT]; GILEAD SCIENCES I) 14 July 2005 (2005-07-14)

D2: WO 2004/072243 A (ENANTA PHARMACEUTICALS INC [US]; MIAO ZENWEI [US]; SUN YING [US]; WU F) 26 August 2004 (2004-08-26)

Methods of treatment:

3.1 Claims 16-21 relate to subject-matter considered by this Authority to be coveredby the provisions of Rule 39.1(iv)/67.1(iv) PCT.

3.2 The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty:

4.1 D1 discloses the compound 5H-imidazo[4,5-c]pyridine, 5-[[6-(2,4-difluorophenyl)-3-pyridazinyl]methyl]-2-(2-fluorophenyl) used to treat HCV (see D1: example 317 page 189; description page 1).

4.2 The compound of claim 5 differs from the example of D1 in that it possesses trifluoromethyl groups in position 2 and 4 of the phenyl ring attached to pyridazine ring, whereas in the example of D1 the said phenyl ring is substituted by fluor atoms at the said positions.

4.3 D2 discloses the compound 3(2H)-pyridazinone, 5-paramethoxyphenyl-5-((2-cyclopropylaminothiazol-4-yl)) used as synthetic intermediate (see D2: compound 186h page 220).

4.4 The compounds of claims 27 differ from the example of D2 in that they possess trifluoromethyl groups in position 2 and 4 of the phenyl ring attached to pyridazine ring, whereas in the example of D1 the said phenyl ring is substituted by a methoxy group at the position 4.

4.5 Thus, the subject-matter of claims 1-27 is novel in the sense of Article 33(2) PCT.

Inventive Step:

5.1 D1 is regarded as the closest prior art for the inventive step assessment of the subject-matter of claims 1-27 and discloses the compound 5H-imidazo[4,5-c]pyridine,5-[[6-(2,4-difluorophenyl)-3-pyridazinyl]methyl]-2-(2-fluorophenyl) used to treat HCV (see D1: example 317 page 189; description page 1).

5.2 The compound of claim 5 differs from the example of D1 in that it possesses trifluoromethyl groups in position 2 and 4 of the phenyl ring attached to pyridazine ring, whereas in the example of D1 the said phenyl ring is substituted by fluor atoms at the said positions.

5.3 The problem to be solved can be regarded as the provision of further compounds to be use to treat HCV.

5.4 The solution proposed by the present application is regarded as involving an inventive step in the sense of Article 33(3) PCT because an anti-HCV replicon activity comparative test provided page 43 in the description shows that the compound of claim 5 is 330 more potent than the cited compound of D1. Thus, the compound of claim 5, its process of preparation and the intermediates used in the said process are inventive.

5.5 Thus, an inventive step can be acknowledged for the subject-matter of claims 1-27.

Industrial Applicability:

6.1 Claims 1-15,22-27 relate to a subject-matter which is considered to have an industrial applicability, and therefore the subject-matter of said claims meets the criteria of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

7.1 The relative term "about" used in claims 20-21 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 111.28PF	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/046477	International filing date *(day/month/year)* 21.12.2005	Priority date *(day/month/year)* 21.12.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D471/04		
Applicant GILEAD SCIENCES, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2006-10-20	16.03.2007
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stroeter, Thomas Telephone No. +49 89 2399-8088

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-16 as originally filed

   Claims, Numbers

   1-5 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3,4

because:

☒ the said international application, or the said claims Nos. 3,4 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-5 YES
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5 YES
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1,2,5 YES

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 3 and 4 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The present application is directed to a compound which is useful in the treatment of viral infections including hepatitis C virus.

2 Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 2004/005286 A (K.U.LEUVEN RESEARCH & DEVELOPMENT; GILEAD SCIENCES, INC; NEYTS, JOHAN;) 15 January 2004

D2: WO 2005/063744 A (K.U. LEUVEN RESEARCH & DEVELOPMENT; PUERSTINGER, GERHARD; GILEAD SCIEN) 14 July 2005

Concerning document D2 please see item VI.

3 The presently claimed compound differs from the structurally closest prior art compounds revealed in D1 which are also antiviral compounds through the phenyloxazolyl group instead of a phenyl or pyridyl group. This structural modification starting from the compounds of D1 in order to solve the problem of providing an alternative antiviral compound useful in the treatment of HCV is not obvious and thus, compound claim 1 and consequently further claims 2-5 appear to be novel (Article 33(2) PCT) and inventive (Article 33(3) PCT).

However, it is remarked that the findings on inventive step are made on condition that experimental data can be provided at a later stage to support that the claimed compound indeed shows the alleged pharmacological effect and as such solves the

problem posed.

4 The subject-matter of the present claims 1, 2 and 5 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present claims 3 and 4 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

The International Search Report mentions P-document D2 which does not form part of the state of the art according to Rule 64.1(b) PCT and thus was not discussed under item V of this report. Since the present priority has been validly claimed, D2 disclosing the compound of example 6 and related subject-matter is not novelty-destroying for present claim 1-5.

Re Item VII
Certain defects in the international application

When entering the regional phase at the EPO, the expression "incorporated by reference" is to be deleted wherever it may appear in the present description.